2001

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SEARCH REQUEST FORM

2A17

Scientific and Technical Information Center

Requester's Full Name: Y. Waddington Examiner #: 68082 Date: 1-10-03
Art Unit: 1614 Phone Number 308-4650 Serial Number: 09/731,139
Mail Box and Bldg/Room Location: CM1 2A17 Results Format Preferred (circle): PAPER DISK E-MAIL

If more than one search is submitted, please prioritize searches in order of need.

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Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: _____

Inventors (please provide full names): Christiane Guitard, Beate Muller, Rebecca Emmons

Earliest Priority Filing Date: _____

***For Sequence Searches Only* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.**

A method for treating condition and diseases associated with IGT or IFG Impaired Glucose Tolerance (IGT) Impaired ~~Fasting~~ Glucose (IFG) with a hypoglycemic agent. The hypoglycemic agent is selected from

nateglinide metformin glictazide
repaglinide tolbutamide glipizide
glimepiride

The diseases are diabetes, dyslipidemia, high blood pressure, uricemia, atherosclerosis, retinopathy, nephropathy

Mary Jane Ruhl
Tech. Info. Specialist, STIC
TC-1600
CM-1, Room 6A-06
Phone: 605-1155

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STAFF USE ONLY	Type of Search	Vendors and cost where applicable
Searcher: Ruhl	NA Sequence (#)	STN
Searcher Phone #:	AA Sequence (#)	Dialog
Searcher Location:	Structure (#)	Questel/Orbit
Date Searcher Picked Up: 1/10/03	Bibliographic	Dr.Link
Date Completed: 1/14/03	Litigation	Lexis/Nexis
Searcher Prep & Review Time:	Fulltext	Sequence Systems
Clerical Prep Time:	Patent Family	WWW/Internet
Online Time:	Other	Other (specify)

PTO-1590 (8-01)

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     FILE 'HCAPLUS' ENTERED AT 13:17:22 ON 14 JAN 2003
                  E GUITARD CHRISTIANE/AU
L1             6 SEA ABB=ON  ("GUITARD C"/AU OR "GUITARD CHRISTIANE"/AU)
                  E MULLER BEATE/AU
L2            35 SEA ABB=ON  ("MULLER BEAT"/AU OR "MULLER BEATE"/AU OR "MULLER
                  BEATRICE U"/AU)
                  E EMMONS REBECCA/AU
L3             7 SEA ABB=ON  ("EMMONS REBECCA"/AU OR "EMMONS REBECCA P"/AU)
L4             1 SEA ABB=ON  L1 AND L2 AND L3

     FILE 'REGISTRY' ENTERED AT 13:21:48 ON 14 JAN 2003
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L5             1 SEA ABB=ON  NATEGLINIDE/CN
                  E REPALINIOLE/CN
L6             1 SEA ABB=ON  REPAGLINIDE/CN
                  E GLIMEPIRIDE/CN
L7             1 SEA ABB=ON  GLIMEPIRIDE/CN
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L8             1 SEA ABB=ON  METFORMIN/CN
                  E TOLBUTAMIDE/CN
L9             1 SEA ABB=ON  TOLBUTAMIDE/CN
                  E GLICLAZIDE/CN
L10            1 SEA ABB=ON  GLICLAZIDE/CN
                  E GLIPIZIDE/CN
L11            1 SEA ABB=ON  GLIPIZIDE/CN
L12            7 SEA ABB=ON  L5 OR L6 OR L7 OR L8 OR L9 OR L10 OR L11

     FILE 'HCAPLUS' ENTERED AT 13:37:48 ON 14 JAN 2003
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                  OR ?FASTING?(W)?GLUCOSE?))
L14         6539 SEA ABB=ON  (L7 OR ?NATEGLINID? OR ?REPAGLINID? OR ?GLIMEPIRIDE
                  ? OR ?METFORMIN? OR ?TOLBUTAMID? OR ?GLICLAZID? OR ?GLIPIZID?)
L15           55 SEA ABB=ON  L13 AND L14
L16           44 SEA ABB=ON  L15 AND (?DIABETES? OR ?DYSLIPIDEMIA? OR ?HYPERLIPI
                  DEMIA? OR ?HIGH?(W)?BLOOD?(W)?PRESSURE? OR ?HYPERTENS? OR
                  ?URICEMIA? OR ?ATHEROSCLER? OR ?ARTERIOSCLER? OR ?RETINOPATH?
                  OR ?NEPHROPATH?)
L17           46 SEA ABB=ON  L13(L)L14
L18           31 SEA ABB=ON  L17(L)(?DIABETES? OR ?DYSLIPIDEMIA? OR ?HYPERLIPIDE
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                  OR ?NEPHROPATH?)

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     14:00:26 ON 14 JAN 2003
L19          180 SEA ABB=ON  L18
L20           99 DUP REMOV L19 (81 DUPLICATES REMOVED)
L21           87 SEA ABB=ON  L20(L)(?TREAT? OR ?THERAP? OR ?PREVENT? OR
                  ?INHIBIT? OR ?CONTROL?)
L22           15 SEA ABB=ON  L21(L) ?METHOD?
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Inventor Search

31 cits from CAPlus

15 cits from other databases

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=> d que stat l18
L7             1 SEA FILE=REGISTRY ABB=ON  GLIMEPIRIDE/CN
L13         2188 SEA FILE=HCAPLUS ABB=ON  (IGT OR IFG OR ?IMPAIR?(W)(?GLUCOSE?(W
                 )?TOLERAN? OR ?FASTING?(W)?GLUCOSE?))
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                 OR ?GLIPIZID?)
L17           46 SEA FILE=HCAPLUS ABB=ON  L13(L)L14
L18           31 SEA FILE=HCAPLUS ABB=ON  L17(L)(?DIABETES? OR ?DYSLIPIDEMIA?
                 OR ?HYPERLIPIDEMIA? OR ?HIGH?(W)?BLOOD?(W)?PRESSURE? OR
                 ?HYPERTENS? OR ?URICEMIA? OR ?ATHEROSCLER? OR ?ARTERIOSCLER?
                 OR ?RETINOPATH? OR ?NEPHROPATH?)

=> d l18 ibib abs hitrn 1-31

L18  ANSWER 1 OF 31  HCAPLUS  COPYRIGHT 2003 ACS
ACCESSION NUMBER:         2002:966704  HCAPLUS
DOCUMENT NUMBER:          138:19354
TITLE:                    Nateglinide improves early insulin secretion and
                          controls postprandial glucose excursions in a
                          prediabetic population
AUTHOR(S):                Saloranta, Carola; Guitard, Christiane; Pecher,
                          Eckhard; De Pablos-Velasco, Pedro; Lahti, Kaj; Brunel,
                          Patrick; Groop, Leif
CORPORATE SOURCE:         Department of Medicine, Helsinki University Hospital,
                          Helsinki, Finland
SOURCE:                   Diabetes Care (2002), 25(12), 2141-2146
                          CODEN: DICAD2; ISSN: 0149-5992
PUBLISHER:                American Diabetes Association, Inc.
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
AB   The purpose of this study was to evaluate the metabolic effectiveness,
     safety, and tolerability of nateglinide in subjects with
     impaired glucose tolerance (IGT) and
     to identify a dose appropriate for use in a diabetes prevention
     study.  This multicenter, double-blind, randomized, parallel-group,
     fixed-dose study of 8 wk' duration was performed in a total of 288
     subjects With IGT using a 2:2:2:1 randomization.  Subjects
     received nateglinide (30, 60, and 120 mg) or placebo before each
     main meal.  Metabolic effectiveness was assessed during a standardized
     meal challenge performed before and after the 8-wk treatment.  All adverse
     events (AEs) were recorded, and confirmed hypoglycemia was defined as
     symptoms accompanied by a self-monitoring of blood glucose measurement
     .ltoreq.3.3 mmol/l (plasma glucose .ltoreq.3.7 mmol/l).
     Nateglinide elicited a dose-related increase of insulin and a
     decrease of glucose during standardized meal challenges, with the
     predominant effect on early insulin release, leading to a substantial
     redn. in peak plasma glucose levels.  Nateglinide was well
     tolerated, and symptoms of hypoglycemia were the only treatment-emergent
     AEs.  Confirmed hypoglycemia occurred in 28 subjects receiving
     nateglinide (30 mg, 0 [0%]; 60 mg, 5 [6.6%]; 120 mg, 23 [26.7%])
     and in 1 (2.3%) subject receiving placebo.  Nateglinide was safe
     and effective in reducing postprandial hyperglycemia in subjects with
     IGT.  Preprandial doses of 30 or 60 mg nateglinide would
     be appropriate to use for longer-term studies to det. whether a
     rapid-onset, rapidly reversible, insulinotropic agent can delay or prevent
     the development of type 2 diabetes.
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REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 2 OF 31 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:666541 HCAPLUS
TITLE: Should patients with polycystic ovarian syndrome be treated with metformin?
AUTHOR(S): Nestler, John E.
CORPORATE SOURCE: Medical College of Virginia, Division of Endocrinology and Metabolism, Virginia Commonwealth University, Richmond, VA, 23298, USA
SOURCE: Human Reproduction (2002), 17(8), 1950-1953
CODEN: HUREEE; ISSN: 0268-1161
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Insulin resistance is a prominent feature of polycystic ovarian syndrome (PCOS), and women with the disorder are at increased risk for the development of other diseases that have been linked to insulin resistance-namely, type 2 **diabetes** and cardiovascular disease. This assocn. between insulin resistance and PCOS must guide the chronic management of the disorder, and accumulating evidence suggests that administration of insulin-sensitizing drugs to individuals at high risk for type 2 **diabetes** decreases the rate of conversion to overt disease. In contrast, limited evidence exists to suggest that oral contraceptive pills-the currently std. therapy for PCOS-may actually decrease insulin sensitivity and induce **impaired glucose tolerance** in women with PCOS. Hence, PCOS should be regarded as a general health issue and the use of insulin-sensitizing drugs such as **metformin** should be considered for the prevention of type 2 **diabetes**.
REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 3 OF 31 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:663102 HCAPLUS
DOCUMENT NUMBER: 137:210317
TITLE: Treatment of polycystic ovary syndrome with insulin-lowering agents
AUTHOR(S): Glueck, Charles J.; Streicher, Patricia; Wang, Ping
CORPORATE SOURCE: Cholesterol Center, Cincinnati, OH, USA
SOURCE: Expert Opinion on Pharmacotherapy (2002), 3(8), 1177-1189
CODEN: EOPHF7; ISSN: 1465-6566
PUBLISHER: Ashley Publications Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. Early diagnosis and therapy of the underlying insulin resistance of heritable polycystic ovary syndrome (PCOS), often manifested at menarche, facilitate the redn. and/or reversal of the reproductive and metabolic morbidity of PCOS, as well as reduce the risk factors for cardiovascular disease. PCOS is characterized by oligoamenorrhea, clin. and biochem. hyperandrogenism, infertility, recurrent miscarriage, insulin resistance, hyperinsulinemia, gestational **diabetes**, **impaired glucose tolerance**, Type 2 **diabetes**, morbid obesity, **hypertension**, hypofibrinolysis, hypertriglyceridemia, low levels of high d. lipoprotein-cholesterol and a sevenfold risk increase in cardiovascular

disease. Insulin sensitizing-lowering agents reduce insulin resistance and hyperinsulinemia, reverse PCOS endocrinopathy and ameliorate the reproductive, metabolic and cardiovascular morbidity of the disorder. The largest literature on the subject discusses **metformin**. Improved pregnancy outcomes in women with PCOS receiving **metformin** may be attributed to its ability to reduce insulin resistance, hyperinsulinemia and hypofibrinolytic plasminogen activator inhibitor activity by the enhancement of folliculogenesis and improvement of oocyte quality.

REFERENCE COUNT: 139 THERE ARE 139 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 4 OF 31 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:581130 HCAPLUS
DOCUMENT NUMBER: 137:149684
TITLE: Metformin & lifestyle intervention prevent type 2 diabetes: Lifestyle intervention has the greater effect
AUTHOR(S): Doggrell, Sheila A.
CORPORATE SOURCE: Department of Physiology and Pharmacology, School of Biomedical Sciences, University of Queensland, 4072, Australia
SOURCE: Expert Opinion on Pharmacotherapy (2002), 3(7), 1011-1013
CODEN: EOPHF7; ISSN: 1465-6566
PUBLISHER: Ashley Publications Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. **Diabetes** mellitus is now occurring in epidemic proportions in many countries. Owing to the limited effectiveness of drug prophylaxis of diabetic complications after **diabetes** has developed, it may be more appropriate to investigate ways to prevent the onset of **diabetes**. A recent trial published by the **Diabetes** Prevention Program Research Group investigated whether lifestyle changes or **metformin** were effective in delaying the onset of **diabetes** in subjects with **impaired glucose tolerance**. The goals of the intensive lifestyle intervention were to achieve and maintain a wt. redn. of 7% through a low-calorie, low-fat diet and to engage in phys. activity of moderate intensity, such as brisk walking, for at least 150 min/wk. The effectiveness of the intensive lifestyle intervention on body wt. was initially quite good but decreased over time. **Metformin** caused some wt. loss but to a lesser extent than the intensive lifestyle intervention. Both therapies decreased the fasting plasma glucose levels to a similar extent initially. The intensive lifestyle intervention decreased plasma glycosylated Hb levels to a greater extent than **metformin**. Both intensive lifestyle intervention and **metformin** reduced the incidence of **diabetes**, with the lifestyle intervention having the greater effect.

REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 5 OF 31 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:574526 HCAPLUS
TITLE: Impaired glucose tolerance and metformin: Clinical and mechanistic aspects
AUTHOR(S): Hermann, Leif Sparre; Wiernsperger, Nicolas
CORPORATE SOURCE: Diabetes Unit, Medical Department, Uddevalla Hospital,

Uddevalla, Swed.
SOURCE: British Journal of Diabetes & Vascular Disease (2002), 2(3), 177-183
CODEN: BJDVAI; ISSN: 1474-6514
PUBLISHER: MediNews (Diabetes) Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The **Diabetes** Prevention Program (DPP) showed that **metformin** reduced the incidence of **diabetes** in subjects with **impaired glucose tolerance** (**IGT**) who were at high risk of progression to type 2 **diabetes**. **Metformin** was not as efficient as intensive life style intervention, but had a clin. significant effect in obese individuals and in those with **impaired fasting glucose** (**IFG**). This review discusses the clin. implications and the mechanistic aspects of the effect of **metformin** in **IGT** and **IFG**. Acute actions of **metformin** on postprandial metab. to improve hepatic glucose handling and improve the lipid profile could contribute to the lower incidence of **diabetes**. Longer term improvements in haemodynamic parameters and reduced oxidative stress are also implicated. **Metformin** offers a potential alternative or complement to lifestyle intervention for **IGT**, and deserves further evaluation in this respect.
REFERENCE COUNT: 90 THERE ARE 90 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 6 OF 31 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:296651 HCAPLUS
DOCUMENT NUMBER: 137:512
TITLE: Metformin therapy in obese adolescents with polycystic ovary syndrome and impaired glucose tolerance: amelioration of exaggerated adrenal response to adrenocorticotropin with reduction of insulinemia/insulin resistance
AUTHOR(S): Arslanian, Silva A.; Lewy, Vered; Danadian, Kapriel; Saad, Rola
CORPORATE SOURCE: Division of Pediatric Endocrinology, Metabolism, Children's Hospital of Pittsburgh, Pittsburgh, PA, 15213, USA
SOURCE: Journal of Clinical Endocrinology and Metabolism (2002), 87(4), 1555-1559
CODEN: JCEMAZ; ISSN: 0021-972X
PUBLISHER: Endocrine Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Functional adrenal hyperandrogenism occurs in women with polycystic ovary syndrome (PCOS). Insulin, similar to its ovarian effect, may impact the regulation of adrenal steroidogenesis by modulating the activity of P450c17.alpha., the rate-limiting enzyme in androgen biosynthesis. We previously demonstrated that obese adolescents with PCOS are severely insulin resistant and are at heightened risk for **impaired glucose tolerance** and type 2 **diabetes**. In the present study we tested the hypothesis that **metformin** therapy in obese adolescents with PCOS will attenuate the adrenal steroidogenic response to ACTH, with redn. of insulin resistance/insulinemia. Fifteen adolescents with PCOS and **impaired glucose tolerance** received 3 mo of **metformin** (850 mg, twice daily) therapy. Pre- and posttherapy they had oral glucose tolerance

testing, ACTH stimulation test, a 3-h hyperinsulinemic (80 mU/m2.cntdot.min)-euglycemic clamp to assess insulin sensitivity and a hyperglycemic clamp to assess insulin secretion. After 3 mo of **metformin** treatment, glucose intolerance improved, with eight subjects having normal glucose tolerance. Total and free T decreased [1.5.+-.0.2 vs. 1.0.+-.0.1 nmol/L (P = 0.022) and 41.3.+-.8.3 vs. 22.2.+-.2.1 pmol/L (P = 0.028), resp.]. Insulin-stimulated glucose disposal increased (21.5.+-.2.2 vs. 25.0.+-.2.2 .mu.mol/kg.cntdot.min; P = 0.041). Fasting insulin and oral glucose tolerance test insulin and glucose area under the curve decreased significantly. ACTH-stimulated increases in androstenedione, 17-hydroxyprogesterone, and 17-hydroxypregnenelone were lower after **metformin** treatment [2.8.+-.0.4 vs. 1.7.+-.0.3 nmol/L (P = 0.014), 7.0.+-.0.6 vs. 5.3.+-.0.5 nmol/L (P = 0.011), and 30.4.+-.3.7 vs. 25.7.+-.4.2 nmol/L (P = 0.054)]. Fasting insulin correlated with the 17-hydroxypregnenelone response to ACTH stimulation (r = 0.52; P = 0.008). In summary, **metformin** treatment of obese adolescents with PCOS and **impaired glucose tolerance** is beneficial in improving glucose tolerance and insulin sensitivity, in lowering insulinemia, and in reducing elevated androgen levels. Moreover, **metformin** therapy is assocd. with attenuation of the adrenal steroidogenic response to ACTH. **Metformin** therapy was well tolerated. In conclusion, double blind, placebo-controlled studies will det. whether insulin-sensitizing therapy corrects not only ovarian hyperandrogenism but also functional adrenal hyperandrogenism in adolescents with PCOS.

REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 7 OF 31 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:78012 HCAPLUS
DOCUMENT NUMBER: 136:288869
TITLE: The NEPI **antidiabetes** study (NANSY). 1: short-term dose-effect relations of **glimepiride** in subjects with **impaired fasting glucose**
AUTHOR(S): Lindblad, U.; Lindwall, K.; Sjostrand, A.; Ranstam, J.; Melander, A.
CORPORATE SOURCE: Skaraborg Institute, Skovde, Swed.
SOURCE: Diabetes, Obesity and Metabolism (2001), 3(6), 443-451
CODEN: DOMEF6; ISSN: 1462-8902
PUBLISHER: Blackwell Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Aim: NANSY is a randomized, placebo-controlled Swedish-Norwegian study which aims to include 2 X 1112 male and female subjects with **impaired fasting glucose** (**IFG**), to assess whether conversion to type 2 **diabetes** can be delayed by addn. of sulfonylurea to dietary regulation and increased exercise. This pilot study was conducted to find the optimum dose of **glimepiride** in NANSY. Methods: In a double blind trial in primary care 25 **IFG** subjects were in random order exposed to single doses and one-week treatments with 0 (placebo), 0.5, 1.0 and 2.0 mg **glimepiride** once daily. The optimum dose was assessed by measuring blood glucose during oral 75 g glucose tolerance test (OGTT), comparing fasting blood glucose, and the area under the blood glucose curve (AUC), and by monitoring hypoglycemic events. Results: With single doses, there was a clear dose-response relationship for the redn. in AUC, with a statistically significant difference only between placebo (mean 1981, 95%

confidence intervals (CI) 1883-2078) and 2 mg **glimepiride** (mean 1763, 95% CI 1665-1861). However, following 1-wk treatments, the only significant difference was between placebo (mean 1934, 95% CI 1856-2012) and 1 mg **glimepiride** (mean 1714, 95% CI 1637-1792). Correspondingly, the only statistically significant difference in fasting blood glucose day 7 was between placebo (5.87 mmol/l, 95% CI 5.68-6.05 mmol/l) and 1 mg **glimepiride** (5.42 mmol/l, 95% CI 5.21-5.62 mmol/l). Chem. hypoglycemia was common but hypoglycemic symptoms were rare and similar between the active doses, and easily countered by the subjects. Conclusions: The sulfonylurea dose-effect curve may be bell-shaped, perhaps due to down regulation of sulfonylurea receptors during chronic exposure. Alternatively, the finding could be a rebound phenomenon, secondary to preceding hypoglycemia. The optimum dose for NANSY was found to be 1 mg **glimepiride**.

IT **93479-97-1, Glimepiride**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(short-term dose-effect relations of **glimepiride** in humans with **impaired fasting glucose** in relation to preventing of type 2 **diabetes**)

REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 8 OF 31 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:723812 HCAPLUS
DOCUMENT NUMBER: 136:63788
TITLE: Diabetogenic effect of cyclosporin A is mediated by interference with mitochondrial function of pancreatic B-cells
AUTHOR(S): Dufer, Martina; Krippeit-Drews, Peter; Lembert, Nicolas; Idahl, Lars-Ake; Drews, Gisela
CORPORATE SOURCE: Department of Pharmacology, Institute of Pharmacy, University of Tubingen, Tubingen, Germany
SOURCE: Molecular Pharmacology (2001), 60(4), 873-879
CODEN: MOPMA3; ISSN: 0026-895X
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Treatment of patients after organ transplantation with the immunosuppressive drug cyclosporin A (CsA) is often accompanied by **impaired glucose tolerance**, thus promoting the development of **diabetes** mellitus. In the present article we show that 2 to 5 .mu.M CsA diminishes glucose-induced insulin secretion of isolated mouse pancreatic islets in vitro by inhibiting glucose-stimulated oscillations of the cytoplasmic free-Ca2+ concn. [Ca2+]c. This effect is not due to an inhibition of calcineurin, which mediates the immunosuppressive effect of CsA, because other calcineurin inhibitors, deltamethrin and tacrolimus, did not affect the oscillations in [Ca2+]c of the B-cells. The CsA-induced decrease in [Ca2+]c to basal values was not caused by a direct inhibition of L-type Ca2+ channels. CsA is known to be a potent inhibitor of the mitochondrial permeability transition pore (PTP), which we recently suggested to be involved in the regulation of oscillations. Consequently, CsA also inhibited the oscillations of the cell membrane potential, and it is shown that these effects could not be ascribed to cellular ATP depletion. However, the mitochondrial membrane potential .DELTA..psi. was affected by CsA by inhibiting the oscillations in .DELTA..psi.. Interestingly, the obsd. redn. in [Ca2+]c could be

counteracted by the K+ATP channel blocker **tolbutamide**, indicating that the stimulus-secretion coupling was interrupted before the closure of K+ATP channels. It is concluded that CsA alters B-cell function by inhibiting the mitochondrial PTP. This terminates the oscillatory activity that is indispensable for adequate insulin secretion. Thus, CsA acts on different targets to induce the immunosuppressive and the diabetogenic effect.

REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 9 OF 31 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:715529 HCAPLUS
DOCUMENT NUMBER: 136:15113
TITLE: Metabolic effects of metformin in patients with impaired glucose tolerance
AUTHOR(S): Lehtovirta, M.; Forsen, B.; Gullstrom, M.; Haggblom, M.; Eriksson, J. G.; Taskinen, M.-R.; Groop, L.
CORPORATE SOURCE: Department of Medicine, Helsinki University Hospital, Helsinki, Finland
SOURCE: Diabetic Medicine (2001), 18(7), 578-583
CODEN: DIMEEV; ISSN: 0742-3071
PUBLISHER: Blackwell Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Aim was to assess the effect of **metformin** on insulin sensitivity, glucose tolerance and components of the metabolic syndrome in patients with **impaired glucose tolerance** (**IGT**). Forty first-degree relatives of patients with Type 2 **diabetes** fulfilling WHO criteria for **IGT** and participating in the Botnia study in Finland were randomized to treatment with either **metformin** 500 mg b.i.d. or placebo for 6 mo. An oral glucose tolerance test (OGTT) and a euglycemic hyperinsulinemic clamp in combination with indirect calorimetry was performed at 0 and 6 mo. The patients were followed after stopping treatment for another 6 mo in an open trial and a repeat OGTT was performed at 12 mo. **Metformin** treatment resulted in a 20% improvement in insulin-stimulated glucose metab. (from 28.7 .+-. 13 to 34.4 .+-. 10.7 .mu.mol/kg fat-free mass (FFM)/min) compared with placebo (P = 0.01), which was primarily due to an increase in glucose oxidn. (from 16.6 .+-. 3.6 to 19.1 .+-. 4.4 .mu.mol/kg FFM; P = 0.03) These changes were assocd. with a minimal improvement in glucose tolerance, which was maintained after 12 mo. **Metformin** improves insulin sensitivity in subjects with **IGT** primarily by reversal of the glucose fatty acid cycle. Obviously large multicenter studies are needed to establish whether these effects are sufficient to prevent progression to manifest Type 2 **diabetes** and assocd. cardiovascular morbidity and mortality.

REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 10 OF 31 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:643992 HCAPLUS
DOCUMENT NUMBER: 136:379854
TITLE: Preventive effect of acarbose and **metformin** on the **IGT** population from becoming **diabetes** mellitus: a 3-year multicentral prospective study
AUTHOR(S): Yang, Wenying; Lin, Lixiang; Qi, Jinwu; Yu, Zhiqing; Pei, Haicheng; He, Guofen; Yang, Zhaojun; Wang, Peng;

Li, Guangwei; Pan, Xiaoren
CORPORATE SOURCE: Department of Endocrinology, China-Japan Friendship Hospital, Beijing, 100029, Peop. Rep. China
SOURCE: Zhonghua Neifenmi Daixie Zazhi (2001), 17(3), 131-134
CODEN: ZNDZEK; ISSN: 1000-6699
PUBLISHER: Shanghaishi Neifenmi Yanjiuso
DOCUMENT TYPE: Journal
LANGUAGE: Chinese
AB The effect of pharmacol. and non-pharmacol. interventions on Chinese subjects with **impaired glucose tolerance** (**IGT**) was studied. In this 3-yr prospective study, 321 subjects aged above 25 yr with **IGT** were included. **IGT** was defined by 1985 WHO criteria utilizing a 75 g oral glucose tolerance test (OGTT). The subjects were divided into control (C), diet plus exercise (D + E), Acarbose (Glucobay; A) and **Metformin** (M) groups. The subjects in the group D + E underwent an individually designed diet and exercise program, the importance of which was reiterated annually. Group C only received conventional education on **diabetes** prevention. The two pharmacol. groups were orally given Acarbose (50 mg, t.i.d) and **Metformin** (0.25 g, t.i.d) resp. OGTT, wt., height, blood pressure, lipids were measured yearly during the follow-up. The t-test, Chi-square test and proportional hazard regression anal. were used to analyze the risk redn. in **diabetes** conversion from each group. The baseline data of the 4 groups had no statistical differences. By the end of study, both the fasting plasma glucose (FPG) and the 2h postprandial plasma glucose (2hPG) in group C elevated (FPG from 6.02 mmol/L to 6.59 mmol/L, 2hPG from 8.83 mmol/L to 9.13 mmol/L), and the annual **diabetes** incidence was 11.6%. The corresponding changes in group D + E were FPG from 6.11 mmol/L to 6.21 mmol/L, PG2h from 9.28 mmol/L to 8.98 mmol/L, and 8.2% of annual **diabetes** incidence. In contrast, both the FPG and the 2hPG significantly decreased in group A (FPG from 6.03 mmol/L to 5.47 mmol/L, 2hPG from 8.34 mmol/L to 7.21 mmol/L) and in group M (FPG from 6.01 mmol/L to 5.47 mmol/L, 2hPG from 9.05 mmol/L to 7.92 mmol/L). The annual **diabetes** incidence decreased to 2.05 in group A, and 4.1% in group M. Proportional hazard regression anal. showed that the annual **diabetes** incidence was pos. correlated with the baseline 2hPG and body mass index (OR=1.33, P=0.006 and OR=1.11, P=0.008, resp.), and neg. correlated with group C and group M (OR=0.12, P=0.0001 and OR=0.23, P=0.0002, resp.). The natural **diabetes** incidence is 11.6% in **IGT** population, and 8.2% in population with conventional diet and exercise interventions; between them there is no significant difference. The pharmacol. interventions with Acarbose or **Metformin** significantly decrease **diabetes** incidence of **IGT** population.

L18 ANSWER 11 OF 31 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:545464 HCAPLUS
DOCUMENT NUMBER: 135:127207
TITLE: Combinations comprising dipeptidylpeptidase-IV inhibitor
INVENTOR(S): Balkan, Boerk; Hughes, Thomas Edward; Holmes, David Grenville; Villhauer, Edwin Bernard
PATENT ASSIGNEE(S): Novartis A.-G., Switz.; Novartis-Erfindungen Verwaltungsgesellschaft m.b.H.
SOURCE: PCT Int. Appl., 46 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001052825	A2	20010726	WO 2001-EP590	20010119
WO 2001052825	A3	20020328		
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM		
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
EP 1248604	A2	20021016	EP 2001-909661	20010119
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR			
BR 2001007715	A	20021119	BR 2001-7715	20010119

PRIORITY APPLN. INFO.:	US 2000-489234	A	20000121
	US 2000-619262	A	20000719
	WO 2001-EP590	W	20010119

OTHER SOURCE(S): MARPAT 135:127207

AB The invention relates to a combination which comprises a DPP-IV inhibitor and at least one further antidiabetic compd., preferably selected from the group consisting of insulin signalling pathway modulators, like inhibitors of protein tyrosine phosphatases (PTPases), non-small mol. mimetic compds. and inhibitors of glutamine-fructose-6-phosphate amidotransferase (GFAT), compds. influencing a dysregulated hepatic glucose prodn., like inhibitors of glucose-6-phosphatase (G6Pase), inhibitors of fructose-1,6-bisphosphatase (F-1,6-BPase), inhibitors of glycogen phosphorylase (GP), glucagon receptor antagonists and inhibitors of phosphoenolpyruvate carboxykinase (PEPCK), pyruvate dehydrogenase kinase (PDHK) inhibitors, insulin sensitivity enhancers, insulin secretion enhancers, .alpha.-glucosidase inhibitors, inhibitors of gastric emptying, insulin, and .alpha.2-adrenergic antagonists, for simultaneous, sep. or sequential use in the prevention, delay of progression or treatment of conditions mediated by dipeptidylpeptidase - IV (DPP-IV), in particular **diabetes**, more esp. type 2 **diabetes** mellitus, conditions of **impaired glucose tolerance** (**IGT**), conditions of impaired fasting plasma glucose, metabolic acidosis, ketosis, arthritis, obesity and osteoporosis; and the use of such combination for the cosmetic treatment of a mammal in order to effect a cosmetically beneficial loss of body wt. Tablets were prepd. contg. **nateglinide**.

L18 ANSWER 12 OF 31 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER:	2001:489226 HCAPLUS
DOCUMENT NUMBER:	135:56079
TITLE:	Use of a hypoglycemic agent for treating impaired glucose metabolism
INVENTOR(S):	Guitard, Christiane; Muller, Beate; Emmons, Rebecca
PATENT ASSIGNEE(S):	Novartis A.-G., Switz.; Novartis-Erfindungen Verwaltungsgesellschaft m.b.H.
SOURCE:	PCT Int. Appl., 26 pp. CODEN: PIXXD2
DOCUMENT TYPE:	Patent

LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001047514	A1	20010705	WO 2000-EP12174	20001204
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1239854	A1	20020918	EP 2000-990641	20001204
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
US 2001016586	A1	20010823	US 2000-731139	20001206
NO 2002002979	A	20020620	NO 2002-2979	20020620

PRIORITY APPLN. INFO.: EP 1999-125761 A 19991223
WO 2000-EP12174 W 20001204

AB The invention discloses the use of a hypoglycemic agent, or a pharmaceutically acceptable salt thereof, for the manuf. of a medicament for the prevention or delay of the progression to overt **diabetes**, esp. type 2, prevention or redn. of microvascular complications (e.g. **retinopathy**, neuropathy, **nephropathy**), prevention or redn. of excessive cardiovascular morbidity (eg. myocardial infarction, arterial occlusive disease, **atherosclerosis** and stroke) and cardiovascular mortality, prevention of cancer and redn. of cancer deaths. Addnl., the invention relates to the use of a treatment for diseases and conditions that are assocd. with impaired glucose metab., **impaired glucose tolerance**, or **impaired fasting glucose**. Formulations of **nateglinide** are included.

REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 13 OF 31 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:223880 HCAPLUS
DOCUMENT NUMBER: 135:178902
TITLE: Role of common sequence variants in insulin secretion in familial type 2 diabetic kindreds: the sulfonylurea receptor, glucokinase, and hepatocyte nuclear factor 1.alpha. genes
AUTHOR(S): Elbein, Steven C.; Sun, Jingping; Scroggin, Eric; Teng, Kui; Hasstedt, Sandra J.
CORPORATE SOURCE: Department of Medicine, Division of Endocrinology, Central Arkansas Veterans Healthcare System and University of Arkansas for Medical Sciences, Little Rock, AR, USA
SOURCE: Diabetes Care (2001), 24(3), 472-478
CODEN: DICAD2; ISSN: 0149-5992
PUBLISHER: American Diabetes Association, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB E have demonstrated high heritability of insulin secretion measured as acute insulin response to glucose times insulin sensitivity (disposition

index). Furthermore, the authors showed that obese normoglycemic family members of a type 2 diabetic proband failed to compensate for the insulin resistance of obesity by increasing insulin secretion. In this study, the authors tested the primary hypotheses that previously described variants in the pancreatic sulfonylurea receptor gene (SUR1 or ABCC8), glucokinase (GCK) gene, or hepatocyte nuclear factor 1.alpha. (TCF1 or HNF1.alpha.) gene contribute to the inherited deficiencies of insulin secretion and .beta.-cell compensation to insulin resistance, as well as the secondary hypotheses that these variants altered insulin sensitivity. The authors typed 124 nondiabetic members of 26 familial type 2 diabetic kindreds who had undergone **tolbutamide**-modified i.v. glucose tolerance tests for 2 variants of the ABCC8 (sulfonylurea) gene, 2 variants of the GCK gene, and 1 common amino acid variant in the TCF1 (HNF1.alpha.) gene. All family members were classified as normal or having **impaired glucose tolerance** based on oral glucose tolerance testing. The authors used minimal model anal. to calc. the insulin sensitivity index (SI) and glucose effectiveness (SG), and acute insulin response to glucose was calcd. as the mean insulin excursion above baseline during the first 10 min after the glucose bolus. Disposition index (DI), a measure of .beta.-cell compensation for insulin sensitivity, was calcd. as insulin sensitivity times acute insulin response. Effects of polymorphisms were detd. using mixed effects models that incorporated family membership and by a likelihood anal. that accounted for family structure through polygenic inheritance. An intronic variant of the ABCC8 gene just upstream of exon 16 was a significant determinant of both DI and an analogous index based on acute insulin response to **tolbutamide** . Surprisingly, heterozygous individuals showed the lowest indexes, whereas the DI in the 2 homozygous states did not differ significantly. Neither the exon 18 variant nor the variants in the GCK and TCF1 genes were significant in this model. However, combined genotypes of ABCC8 exon 16 and 18 variants again significantly predicted both indexes of glucose and **tolbutamide**-stimulated insulin secretion. Unexpectedly, a variant in the 3' untranslated region of the GCK gene interacted significantly with BMI to predict insulin sensitivity. The exon 16 variant of the ABCC8 gene reduced .beta.-cell compensation to the decreased insulin sensitivity in the heterozygous state. This may explain the observation from several groups of an assocn. of the ABCC8 variants in **diabetes** and is consistent with other studies showing a role of ABCC8 variants in pancreatic .beta.-cell function. However, this study focused on individuals from relatively few families. Ascertainment bias, family structure, and other interacting genes might have influenced this unexpected result. Addnl. studies are needed to replicate the obsd. deficit in .beta.-cell compensation in individuals heterozygous for ABCC8 variants. Likewise, the role of the GCK 3' variant in the reduced insulin sensitivity of obesity will require further study.

REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 14 OF 31 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:126492 HCAPLUS
DOCUMENT NUMBER: 134:305168
TITLE: Increased PAI-1 and tPA antigen levels are reduced with metformin therapy in HIV-infected patients with fat redistribution and insulin resistance
AUTHOR(S): Hadigan, C.; Meigs, J. B.; Rabe, J.; D'Agostino, R. B.; Wilson, P. W. F.; Lipinska, I.; Tofler, G. H.; Grinspoon, S.
CORPORATE SOURCE: Neuroendocrine Unit, Massachusetts General Hospital,

Harvard Medical School, Boston, MA, 02114, USA
SOURCE: Journal of Clinical Endocrinology and Metabolism (2001), 86(2), 939-943
CODEN: JCEMAZ; ISSN: 0021-972X
PUBLISHER: Endocrine Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Cardiovascular disease (CVD) risk assocd. with fat redistribution seen among HIV-infected individuals remains unknown, but may be increased due to **hyperlipidemia**, hyperinsulinemia, increased visceral adiposity, and a prothrombotic state assocd. with these metabolic abnormalities. In this study we characterized plasminogen activator inhibitor-1 (PAI-1) and tissue-type plasminogen activator (tPA) antigen levels, markers of fibrinolysis and increased CVD risk, in HIV lipodystrophic patients compared to controls. Furthermore, we investigated the effect of treatment with **metformin** on PAI-1 and tPA antigen levels in patients with HIV-assocd. fat redistribution. Eighty-six patients (age 43.+-.1 yr, BMI 26.1.+-.0.5 kg/m2) with HIV and fat redistribution were compared to 258 age- and BMI-matched subjects from the Framingham Offspring study. In addn., 25 HIV-infected patients with fat redistribution and fasting insulin > 15 .mu.U/mL [104 pmol/L] or **impaired glucose tolerance**, but without **diabetes** mellitus were enrolled in a placebo-controlled treatment study of **metformin** 500mg twice daily. PAI-1 and tPA antigen levels were significantly increased in patients with HIV related fat redistribution compared to Framingham control subjects (46.1.+-.1.4 vs. 18.9.+-.0.9 .mu.g/L PAI-1, 16.6.+-.0.8 vs. 8.0.+-.0.3 .mu.g/L tPA, P=0.0001). Among patients with HIV infection, a multivariate regression anal. including age, sex, waist-to-hip ratio, BMI, smoking status, protease inhibitor use and insulin area under the curve (AUC), found gender and insulin AUC were significant predictors of tPA antigen. Twelve weeks of **metformin** treatment resulted in decreased tPA antigen levels (-1.9.+-.1.4 vs. +1.4.+-.1.0 .mu.g/L in the placebo-treated group P=0.02). Similarly, **metformin** resulted in improvement in PAI-1 levels (-8.7.+-.2.3 vs. +1.7.+-.2.9 .mu.g/L, P=0.03). Change in insulin AUC correlated significantly with change in tPA antigen (r=0.43, P=0.03). PAI-1 and tPA antigen, markers of impaired fibrinolysis and increased CVD risk, are increased in assocn. with hyperinsulinemia in patients with HIV and fat redistribution. **Metformin** reduces PAI-1 and tPA antigen concns. in these patients and may ultimately improve assocd. CVD risk.

REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 15 OF 31 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:822207 HCAPLUS
DOCUMENT NUMBER: 135:28884
TITLE: The diabetes prevention program: Baseline characteristics of the randomized cohort
CORPORATE SOURCE: The Diabetes Prevention Program Research Group, Diabetes Prevention Program Coordinating Center, the Biostatistics Center, George Washington University, Rockville, MD, 20852, USA
SOURCE: Diabetes Care (2000), 23(11), 1619-1629
CODEN: DICAD2; ISSN: 0149-5992
PUBLISHER: American Diabetes Association, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The **Diabetes** Prevention Program (DPP) is a 27-center randomized

clin. trial designed to evaluate the safety and efficacy of interventions that may delay or prevent development of **diabetes** in people at increased risk for type 2 **diabetes**. Eligibility requirements were age .gtoreq.25 yr, BMI .gtoreq.24 kg/m2 (.gtoreq.22 kg/m2 for Asian-Americans), and **impaired glucose tolerance** plus a fasting plasma glucose of 5.3-6.9 mmol/l (or .ltoreq.6.9 mmol for American Indians). Randomization of participants into the DPP over 2.7 yr ended in June 1999. Baseline data for the three treatment groups-intensive lifestyle modification, std. care plus **metformin**, and std. care plus placebo-are presented for the 3,234 participants who have been randomized. Of all participants, 55% were Caucasian, 20% were African-American, 16% were Hispanic, 5% were American Indian, and 4% were Asian-American. Their av. age at entry was 51.+-.10.7 yr (mean .+-. SD), and 67.7% were women. Moreover, 16% were <40 yr of age, and 20% were .gtoreq.60 yr of age. Of the women, 48% were postmenopausal. Men and women had similar frequencies of history of hypercholesterolemia (37 and 33%, resp.) or **hypertension** (29 and 26%, resp.). On the basis of fasting lipid detns., 54% of men and 40% of women fit National Cholesterol Education Program criteria for abnormal lipid profiles. More men than women were current or former cigarette smokers or had a history of coronary heart disease. Furthermore, 66% of men and 71% of women had a first degree relative with **diabetes**. Overall, BMI averaged 34.0.+-.6.7 kg/m2 at baseline with 57% of the men and 73% of women having a BMI .gtoreq.30 kg/m2. Av. fasting plasma glucose (6.0.+-.0.5 mmol/l) and HbAlc (5.9.+-.0.5%) in men were comparable with values in women (5.9.+-.0.4 mmol/l and 5.9.+-.0.5%, resp.). The DPP has successfully randomized a large cohort of participants with a wide distribution of age, obesity, and ethnic and racial backgrounds who are at high risk for developing type 2 **diabetes**. The study will examine the effects of interventions on the development of **diabetes**.

REFERENCE COUNT: 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 16 OF 31 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:359514 HCAPLUS
DOCUMENT NUMBER: 133:114898
TITLE: Response of pancreatic .beta.-cells to improved insulin sensitivity in women at high risk for type 2 diabetes
AUTHOR(S): Buchanan, Thomas A.; Xiang, Anny H.; Peters, Ruth K.; Kjos, Siri L.; Berkowitz, Kathleen; Marroquin, Aura; Goico, Jose; Ochoa, Cesar; Azen, Stanley P.
CORPORATE SOURCE: Departments of Medicine, Obstetrics and Gynecology, University of Southern California School of Medicine, Los Angeles, CA, USA
SOURCE: Diabetes (2000), 49(5), 782-788
CODEN: DIAEAZ; ISSN: 0012-1797
PUBLISHER: American Diabetes Association
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The purpose of this study was to examine the response of pancreatic .beta.-cells to changes in insulin sensitivity in women at high risk for type 2 **diabetes**. Oral glucose tolerance tests (OGTTs) and frequently sampled i.v. glucose tolerance tests (FSIGTs) were conducted on Latino women with **impaired glucose tolerance** and a history of gestational **diabetes** before and after 12 wk of treatment with 400 mg/day troglitazone (n = 13) or placebo (n = 12).

Insulin sensitivity was assessed by minimal model anal., and .beta.-cell insulin release was assessed as acute insulin responses to glucose (AIRg) and **tolbutamide** (AIRt) during FSIGTs and as the 30-min incremental insulin response (30-min dINS) during OGTTs. .beta.-Cell compensation for insulin resistance was assessed as the product (disposition index) of minimal model insulin sensitivity and each of the 3 measures of .beta.-cell insulin release. In the placebo group, there was no significant change in insulin sensitivity or in any measure of insulin release, .beta.-cell compensation for insulin resistance, or glucose tolerance. Troglitazone treatment resulted in a significant increase in insulin sensitivity, as reported previously. In response, AIRg did not change significantly, so that the disposition index for AIRg increased significantly from baseline (P = 0.004) and compared with placebo (P = 0.02). AIRt (P = 0.001) and 30-min dINS (P = 0.02) fell with improved insulin sensitivity during troglitazone treatment, so that the disposition index for each of these measures of .beta.-cell function did not change significantly from baseline (P > 0.20) or compared with placebo (P > 0.3). Minimal model anal. revealed that 89% of the change from baseline in insulin sensitivity during troglitazone treatment was accounted for by lowered plasma insulin concns. Neither oral nor i.v. glucose tolerance changed significantly from baseline or compared with placebo during troglitazone treatment. The predominant response of .beta.-cells to improved insulin sensitivity in women at high risk for type 2 **diabetes** was a redn. in insulin release to maintain nearly const. glucose tolerance.

REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 17 OF 31 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:794088 HCAPLUS
DOCUMENT NUMBER: 132:18405
TITLE: Clinical efficacy of metformin against insulin resistance parameters: Sinking the iceberg
AUTHOR(S): Zimmet, Paul; Collier, Greg
CORPORATE SOURCE: International Diabetes Institute, Melbourne, Australia
SOURCE: Drugs (1999), 58(Suppl. 1), 21-28
CODEN: DRUGAY; ISSN: 0012-6667
PUBLISHER: Adis International Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 47 refs. It has been increasingly recognized in recent years that type 2 (non-insulin-dependent) **diabetes** is part of a cluster of cardiovascular risk factors known as the metabolic syndrome, but also endorsed with such names as the deadly quartet, syndrome X and the insulin resistance syndrome. **Atherosclerosis** is the most common complication of type 2 **diabetes** among Europeans, and coronary artery, cerebrovascular and peripheral vascular disease are 2 to 5 times more common in people with this condition than in those without **diabetes**. These observations indicate that the treatment of type 2 **diabetes** requires agents that do more than simply lower blood glucose levels, and a therapy with both antihyperglycemic effects and beneficial effects on **dyslipidemia, hypertension,** obesity, hyperinsulinemia and insulin resistance is likely to be most useful. In this respect, **metformin** has an important and established role: this drug has been shown to lower blood glucose and triglyceride levels, and to assist with wt. redn. and to reduce hyperinsulinemia and insulin resistance. Studies in the Israeli sand rat, Psammomys obesus, have indicated hyper-insulinemia/insulin resistance to

be the initial and underlying metabolic disorder in obesity and type 2 **diabetes**. Thus, the well established effect of **metformin** in reducing insulin resistance makes this drug an excellent candidate for the prevention of progression of **impaired glucose tolerance** to type 2 **diabetes**, and for the redn. of mortality assocd. with cardiovascular disease.

REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 18 OF 31 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:764924 HCAPLUS
DOCUMENT NUMBER: 132:216888
TITLE: Effect of metformin on impaired glucose tolerance (IGT) patients
AUTHOR(S): Li, Chunlin; Pan, Changyu; Lu, Juming; Zhu, Yan; Wang, Jianhua; Deng, Xinxin; Xia, Fengcheng; Wang, Hengzhu; Wang, Hengyu
CORPORATE SOURCE: The General Hospital of PLA, Beijing, 100853, Peop. Rep. China
SOURCE: Jiefangjun Yixue Zazhi (1999), 24(2), 107-109
CODEN: CFCHBN; ISSN: 0577-7402
PUBLISHER: Jenminjun Chubanshe
DOCUMENT TYPE: Journal
LANGUAGE: Chinese
AB To evaluate the effects of **metformin** on glucose metab., insulin sensitivity and conversion rate of **diabetes** mellitus (DM) in **IGT** patients; 70 subjects with **IGT** were given **metformin** or placebo for one year in a double-blind, placebo-controlled study. The results showed that, in **metformin** group, 1 **IGT** patient converted into DM (3.0%), 4 remained unchanged (12.1%) and 28 became normal (84.9%) after one-year **metformin** treatment, while, in placebo group, above data were 6(16.2%), 12(32.4%) and 19(51.4%), resp., (P = 0.011). **Metformin** treatment was assocd. with improvement of fasting blood glucose concn. and insulin activity index. Urinary albumin excretion, waist/hip ratio and body mass index were also decreased with statistical significance as compared with placebo group. **Metformin** might have some benefit in intervention of **IGT** patients.

L18 ANSWER 19 OF 31 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:477477 HCAPLUS
DOCUMENT NUMBER: 131:139288
TITLE: Effect of metformin on patients with impaired glucose tolerance
AUTHOR(S): Li, C. L.; Pan, C. Y.; Lu, J. M.; Zhu, Y.; Wang, J. H.; Deng, X. X.; Xia, F. C.; Wang, H. Z.; Wang, H. Y.
CORPORATE SOURCE: Department of Endocrinology, Chinese PLA General Hospital, Beijing, 100853, Peop. Rep. China
SOURCE: Diabetic Medicine (1999), 16(6), 477-481
CODEN: DIMEEV; ISSN: 0742-3071
PUBLISHER: Blackwell Science
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effect of **metformin** on glucose metab., insulin sensitivity and rate of conversion **diabetes** was evaluated in people with **impaired glucose tolerance** (**IGT**). Seventy subjects with **IGT** were randomized under double-blind conditions to receive either placebo (n = 37) or **metformin** (n =

33) at a dosage of 250 mg three times daily for a duration of 12 mo. Glycemic control, plasma insulin and other biochem. indexes were assessed before and after 3, 6 and 12 mo. At 12 mo the conversion rate to **diabetes** was 16.2% in the placebo group compared to 3.0% for the **metformin** group (P = 0.011). Of subjects treated with **metformin** for 12 mo, 84.9% became normoglycemic compared to 51.4% of those receiving the placebo. Significant improvements in fasting glucose, glucose tolerance and insulin sensitivity were found at 12 mo and at intermediate clinic assessments. **Metformin** can improve glucose metab. in **IGT** patients and may be a treatment option in their management of **IGT** subjects.

REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 20 OF 31 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:473639 HCAPLUS
DOCUMENT NUMBER: 131:345943
TITLE: Thiazolidinediones: a new class of antidiabetic drugs
AUTHOR(S): Day, C.
CORPORATE SOURCE: Diabetes Research Group, Life and Health Sciences, Aston University, Birmingham, B4 7ET, UK
SOURCE: Diabetic Medicine (1999), 16(3), 179-192
CODEN: DIMEEV; ISSN: 0742-3071
PUBLISHER: Blackwell Science
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 140 refs. Thiazolidinediones (TZDs) are a new class of oral antidiabetic agents. They selectively enhance or partially mimic certain actions of insulin, causing a slowly generated antihyperglycemic effect in Type 2 (non-insulin-dependent) diabetic patients. This is often accompanied by a redn. in circulating concns. of insulin, triglycerides and nonesterified fatty acids. TZDs act additively with other types of oral antidiabetic agents (sulfonylureas, **metformin** and acarbose) and reduce the insulin dosage required in insulin-treated patients. The glucose-lowering effect of TZDs is attributed to increased peripheral glucose disposal and decreased hepatic glucose output. This is achieved substantively by the activation of a specific nuclear receptor - the peroxisome proliferator-activated receptor-.gamma., which increases transcription of certain insulin-sensitive genes. To date one TZD, troglitazone, has been introduced into clin. use (in Japan, the USA and the UK in 1997). This was suspended after 2 mo in the UK pending further investigation of adverse effects on liver function. TZDs have been shown to improve insulin sensitivity in a range of insulin-resistant states including obesity, **impaired glucose tolerance** and polycystic ovary syndrome. In Type 2 **diabetes**, the TZDs offer a new type of oral therapy to reduce insulin resistance and assist glycemic control.

REFERENCE COUNT: 140 THERE ARE 140 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 21 OF 31 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:248864 HCAPLUS
TITLE: Heritability of pancreatic .beta.-cell function among nondiabetic members of caucasian familial type 2 diabetic kindreds
AUTHOR(S): Elbein, Steven C.; Hasstedt, Sandra J.; Wegner, Kimberley; Kahn, Steven E.

CORPORATE SOURCE: Endocrinology Section, John L. McClellan Memorial Veterans Affairs Hospital, Little Rock, AR, 72205, USA
SOURCE: J. Clin. Endocrinol. Metab. (1999), 84(4), 1398-1403
CODEN: JCEMAZ; ISSN: 0021-972X
PUBLISHER: Endocrine Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Both defective insulin secretion and insulin resistance have been reported in relatives of type 2 diabetic subjects. We tested 120 members of 26 families with a type 2 diabetic sibling pair with a **tolbutamide** -modified, frequently sampled iv glucose tolerance test to det. the insulin sensitivity index (SI) and acute insulin response to glucose (AIRglucose). A measure of .beta.-cell compensation for insulin sensitivity was calcd. as the product SI .times. AIRglucose, based on the demonstrated hyperbolic relationship between insulin sensitivity and insulin secretion. A percentile score for this compensation was assigned based on published values. Of the 120 family members, 26 had previously diagnosed **impaired glucose tolerance** on oral testing, and 94 had normal glucose tolerance tests. As a group, family members showed a significantly lower SI .times. AIRglucose than a similar, previously reported, control population, even when **impaired glucose tolerance** members were excluded. We performed a multivariate anal. of **diabetes** status, SI, AIRglucose, and to est. the heritability of each trait and the genetic and environmental correlations between traits. We estd. the heritability of SI .times. AIRglucose to be 67 .+-. 3% when all members were included and 70 .+-. 4% when only normal glucose tolerance members were considered. Both AIRglucose and SI were also familial, albeit with lower heritabilities (38 .+-. 1% and 38 .+-. 2%, resp., for all family members). Both SI .times. AIRglucose and SI showed strong neg. genetic correlations with **diabetes** (-85 .+-. 3% and -87 .+-. 2%, resp., all family members), whereas AIRglucose did not correlate with **diabetes**. We conclude that insulin secretion, as measured by SI .times. AIRglucose, is decreased in nondiabetic members of familial type 2 diabetic kindreds, that SI .times. AIRglucose in these high risk families is highly heritable, and that the same polygenes may det. **diabetes** status and a low SI .times. AIRglucose. Our data suggest that insulin secretion, when expressed as an index normalized for insulin sensitivity, is more familial than either insulin sensitivity or first phase insulin secretion alone and may be a very useful trait for identifying genetic predisposition to type 2 **diabetes**.

REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 22 OF 31 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:23649 HCAPLUS
DOCUMENT NUMBER: 130:64401
TITLE: Insulin resistance, impaired glucose tolerance and non-insulin-dependent diabetes, pathologic mechanisms and treatment. Current status and therapeutic possibilities
AUTHOR(S): Turner, Nicholas C.; Clapham, John C.
CORPORATE SOURCE: SmithKline Beecham Pharmaceuticals, Harlow, CM19 5AW, UK
SOURCE: Progress in Drug Research (1998), 51, 33-94
CODEN: FAZMAE; ISSN: 0071-786X
PUBLISHER: Birkhaeuser Verlag
DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review with 370 refs. is given on the current status and therapeutic possibilities of insulin resistance, **impaired glucose tolerance**, and non-insulin-dependent **diabetes**. The biochem. and mol. nature of the defects in insulin sensitivity and glucose uptake are reviewed and some of the potential causative mechanisms are dicussed. The genetic and environmental basis of insulin resistance is presented, and potential therapeutic targets are discussed including thiazolidinediones, **metformin**, dehydroepiandrosterone analogs, antiglucocorticoids, inhibitors of tumor necrosis factor .alpha., and anti-obesity agents. Only combination therapies involving agents addressing insulin resistance, insulin secretion, hepatic glucose output, and obesity will provide multiple treatment regimes for effective disease management.

REFERENCE COUNT: 370 THERE ARE 370 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 23 OF 31 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1998:780865 HCAPLUS

DOCUMENT NUMBER: 130:148505

TITLE: Effect of gliclazide treatment on insulin secretion and .beta.-cell mass in non-insulin dependent diabetic Goto-Kakisaki rats

AUTHOR(S): Dachicourt, Nathalie; Bailbe, Danielle; Gangnerau, Marie-Noelle; Serradas, Patricia; Ravel, Denis; Portha, Bernard

CORPORATE SOURCE: CNRS ESA 7059, Lab. Physiopathology of Nutrition, Universite Paris 7/D. Diderot, Paris, 75251, Fr.

SOURCE: European Journal of Pharmacology (1998), 361(2/3), 243-251
CODEN: EJPHAZ; ISSN: 0014-2999

PUBLISHER: Elsevier Science B.V.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The Goto-Kakisaki rat is a genetic non-overweight model of non-insulin-dependent **diabetes** mellitus. Adult Goto-Kakisaki rats exhibit a mild basal hyperglycemia (11 mmol/l) with **impaired glucose tolerance**, elevated basal plasma insulin level, a failure of insulin release in response to glucose together with a 50% depletion of the total pancreatic .beta.-cell mass and insulin stores. We have examd. the effects of long-term (4 wk) **gliclazide** treatment on the severity of **diabetes** in adult male Goto-Kakisaki rats (10-12 wk of age). **Gliclazide** was administered orally (10 mg/kg per day). **Gliclazide**-treated Goto-Kakisaki rats were evaluated against Wistar and untreated Goto-Kakisaki rats. In the **gliclazide**-treated Goto-Kakisaki rats, basal plasma glucose levels declined progressively reaching 8 mmol/l as a mean at the end of treatment, and their basal insulin levels decreased to values similar to those in non-diabetic Wistar rats. Despite their total pancreatic .beta.-cell remaining unaffected, their pancreatic insulin stores were twice increased, with a similar improvement of the insulin content per individual .beta.-cell. Furthermore, the glucose-stimulated insulin release as evaluated in vivo during an i.v. glucose tolerance test was significantly improved (twice increased) in the **gliclazide** -treated Goto-Kakisaki rats. This was correlated with a modest but significant enhancement of the early phase of insulin release in vitro (isolated perfused pancreas), in response to glucose. However, the

overall insulin response in vitro remained clearly defective with no reappearance of the late phase of insulin release. The in vitro response to arginine (which was basically amplified in the Goto-Kakisaki model) or to **gliclazide** were kept unchanged after the **gliclazide** treatment. In conclusion, chronic **gliclazide** does not exert any .beta.-cytotrophic effect, but improves .beta.-cell function in the adult Goto-Kakisaki rat as far as it lowers basal insulin release, increases .beta.-cell insulin stores, and increases the glucose-induced insulin release.

REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 24 OF 31 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:635939 HCAPLUS
DOCUMENT NUMBER: 127:272125
TITLE: Pathophysiology of type 2 diabetes and modes of action of therapeutic interventions
AUTHOR(S): Dagogo-Jack, Samuel; Santiago, Julio V.
CORPORATE SOURCE: Division of Endocrinology, Diabetes, and Metabolism, Department of Medicine, Washington University School of Medicine, St Louis, MO, USA
SOURCE: Archives of Internal Medicine (1997), 157(16), 1802-1817
CODEN: AIMDAP; ISSN: 0003-9926
PUBLISHER: American Medical Association
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 181 refs. At least 90% of the 12 to 15 million persons with **diabetes** mellitus in the United States, half of whose condition remains undiagnosed, have type 2 **diabetes**. Type 2 **diabetes** is preceded by a long period of **impaired glucose tolerance**, a reversible metabolic state assocd. with increased prevalence of macrovascular complications. Thus, at the time of diagnosis, long-term complications have developed in almost one fourth of patients. Susceptibility to type 2 **diabetes** requires genetic (most likely polygenic) and acquired factors, and its pathogenesis involves an interplay of progressive insulin resistance and beta-cell failure. The ideal treatment of type 2 **diabetes** should reverse insulin resistance and beta-cell dysfunction in most treated patients and prevent, delay, or reverse long-term complications. Current strategies are aimed at amelioration of insulin resistance (diet, exercise, wt. loss, and **metformin** and troglitazone therapy), augmentation of insulin supply (sulfonylurea and insulin therapy), or limitation of postprandial hyperglycemia (acarbose therapy). Future therapies probably will target (1) insulin resistance, using a multifaceted approach; (2) hepatic glucose prodn., using gluconeogenesis inhibitors; (3) excess nonesterified fatty acid prodn., using lipolysis inhibitors; and (4) fat oxidn., using carnitine palmitoyltransferase I and II inhibitors. Attempts also could be made to stimulate energy expenditure and increase nonoxidative glucose disposal by means of .beta.3-adrenoceptor agonists. One promising strategy is an attack on multiple pathophysiol. processes by combining antidiabetic agents with disparate mechanisms of action. Thus, we now have unprecedented resources for drug therapy for **diabetes**, with great opportunity for innovative combinations. It is hoped that these expanded choices will provide the tools necessary for a more efficient management of type 2 **diabetes** and prevention of its long-term complications.

L18 ANSWER 25 OF 31 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:494991 HCAPLUS
DOCUMENT NUMBER: 127:144622
TITLE: Trivalent chromium and the diabetes prevention program
AUTHOR(S): Linday, L. A.
CORPORATE SOURCE: The College of Physicians and Surgeons, New York, NY, 10019, USA
SOURCE: Medical Hypotheses (1997), 49(1), 47-49
CODEN: MEHYDY; ISSN: 0306-9877
PUBLISHER: Churchill Livingstone
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 20 refs. The **Diabetes** Prevention Program is a new, 150 million dollar, NIH-sponsored study designed to det. whether non-insulin-dependent **diabetes** mellitus can be prevented or delayed in persons with **impaired glucose tolerance**. Four thousand subjects will be randomly assigned to one of four study groups and followed for 4.5 yr. Study groups include intensive lifestyle intervention with diet and exercise; **metformin** (Glucophage.RTM.) or troglitazone (an investigational drug) with std. diet and exercise; and a control group. Insulin resistance is an important pathogenic factor in **impaired glucose tolerance**. Trivalent chromium, a dietary supplement that potentiates the action of insulin, was not included in the program. Like **metformin** and troglitazone, trivalent chromium decreases insulin resistance and has an acceptable side-effect profile; furthermore, it is available at a fraction of their cost. Trivalent chromium should have been included in the **Diabetes** Prevention Program; it is unfortunate that it was omitted.

L18 ANSWER 26 OF 31 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:477544 HCAPLUS
DOCUMENT NUMBER: 122:230526
TITLE: Normalization of impaired glucose tolerance by the short-acting hypoglycemic agent calcium (2S)-2-benzyl-3-(cis-hexahydro-2-isoindolinylcarbonyl)propionate dihydrate (KAD-1229) in non-insulin-dependent diabetes mellitus rats
AUTHOR(S): Ohnota, Hideki; Koizumi, Takashi; Kobayashi, Miho; Momose, Yasunori; Sato, Fumiyasu
CORPORATE SOURCE: Pharmaceutical Laboratory, Kissei Pharmaceutical Co. Ltd., Nagano, 399-83, Japan
SOURCE: Canadian Journal of Physiology and Pharmacology (1995), 73(1), 1-6
CODEN: CJPPA3; ISSN: 0008-4212
PUBLISHER: National Research Council of Canada
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The authors have investigated the hypoglycemic effects of the newly synthesized short-acting nonsulfonylurea hypoglycemic agent calcium (2S)-2-benzyl-3-(cis-hexahydro-2-isoindolinylcarbonyl)-propionate dihydrate (KAD-1229) in non-insulin-dependent **diabetes** mellitus (NIDDM) rats. NIDDM rats that were given a neonatal injection of 60 mg/kg streptozotocin showed a dose-dependent but attenuated response to oral administration of KAD-1229 and **gliclazide**, and their **impaired glucose tolerance** was improved but not normalized. The authors next produced, using a neonatal injection of 30 mg/kg streptozotocin, a mild type of NIDDM rat with less

impaired glucose tolerance. These rats responded well to these insulinotropic hypoglycemic agents. Their impaired glucose and meal tolerance were completely normalized by oral administration of 3 mg/kg KAD-1229. The efficacy of KAD-1229 in this NIDDM rat model 1-3 h after oral glucose administration was comparable with similar doses of **gliclazide**, despite its shorter hypoglycemic action (compared with **gliclazide**), in fasting normal rats. In meal tolerance tests (20 kcal/kg; 1 cal = 4.2 J), KAD-1229 reduced abnormally enhanced plasma glucose levels 1-3 h after administration. This effect disappeared by 5 h. In contrast, **gliclazide** showed sustained hypoglycemic effects until 5 h after oral administration, with a lower postprandial (0.5-1 h) effect. These data indicated that the rapid- and short-acting efficacy of KAD-1229 would be beneficial and sufficient to control postprandial plasma glucose in NIDDM rats.

L18 ANSWER 27 OF 31 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1994:401158 HCAPLUS
DOCUMENT NUMBER: 121:1158
TITLE: Immunoradiometric assay of human intact proinsulin applied to patients with type 2 diabetes, impaired glucose tolerance, and hyperandrogenism
AUTHOR(S): Chevenne, Didier; Ruiz, Juan; Lohmann, Laurence; Laudat, Antoine; Leblanc, Herve; Gray, I. Peter; Passa, Philippe; Porquet, Dominique
CORPORATE SOURCE: Lab. Biochim.-Hormonol., Hop. Robert Debre, Paris, 75019, Fr.
SOURCE: Clinical Chemistry (Washington, DC, United States) (1994), 40(5), 754-7
CODEN: CLCHAU; ISSN: 0009-9147
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The authors describe an immunoradiometric assay for human intact proinsulin in serum. In this method, one monoclonal antibody, coated onto polyacrylamide beads, cross-reacts with proinsulins and insulin. A sandwich is formed with intact proinsulin, split (65-66)proinsulin, and des(64-65)-proinsulin binding with an 125I-labeled monoclonal antibody specific for an epitope at the intact B-C junction of proinsulin. Because split-(65-66) and des(64-65)-proinsulin concns. are very low in serum, this assay essentially measures intact proinsulin. When the authors used 1-mL serum samples, the mean detection limit was 0.4 pmol/L. Mean proinsulin concns. (pmol/L) were 3.4 in healthy fasting subjects, 28.5 in patients with type 2 **diabetes** (treated with **metformin** and sulfonylureas), 5.0 in women with hyperandrogenism and normal insulinemia, 10.3 in women with hyperandrogenism and hyperinsulinemia, and 8.5 in patients with **impaired glucose tolerance**.

L18 ANSWER 28 OF 31 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1983:87174 HCAPLUS
DOCUMENT NUMBER: 98:87174
TITLE: Insulin and glucagon secretion in BB Wistar rats with impaired glucose tolerance
AUTHOR(S): Nakhooda, A. F.; Poussier, P.; Marliss, E. B.
CORPORATE SOURCE: Dep. Med., Univ. Toronto, Toronto, ON, Can.
SOURCE: Diabetologia (1983), 24(1), 58-62
CODEN: DBTGAJ; ISSN: 0012-186X
DOCUMENT TYPE: Journal

LANGUAGE: English
AB Glucose tolerance and insulin secretion were studied in nondiabetic littermates of BB diabetic rats, aged 4-6 mo. Initial screening involved 2 i.p. glucose tolerance tests (0.2 g/100 g body wt.) performed 1 wk apart. Nineteen rats (12%) had impaired tolerance which persisted in 14 (74%) (group 1) and was transient in 5 animals (group 2). Seven rats progressed to overt **diabetes** in group 1, but none in group 2. Group 1 was characterized by (a) sustained abnormalities in glucose response to oral and i.p. glucose, as well as i.p. **tolbutamide** and arginine; (b) fasting hypoinsulinemia; (c) decreased insulin response to glucose and **tolbutamide**; (d) suppression of the early and late phases of immunoreactive insulin response to i.v. glucose; (e) no systematic abnormalities in glucagon secretion; and (f) the presence of significant insulitis. The group 2 rats had (a) normal glycemic response to oral and i.p. glucose, **tolbutamide**, and arginine on further testing; (b) normal fasting insulin but excessive insulin response to glucose and **tolbutamide**, but not to arginine, and (c) mainly normal islet morphol. Thus, **impaired glucose tolerance** may occur in BB rats with either hypoinsulinemia or hyperinsulinemia.

L18 ANSWER 29 OF 31 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1977:137396 HCAPLUS
DOCUMENT NUMBER: 86:137396
TITLE: Insulin response to glucose or glucagon in subclinical diabetes previously injected with tolbutamide
AUTHOR(S): Ohneda, Akira; Watanabe, Kiyoshi; Maruhama, Yoshisuke; Itabashi, Hiroshi; Horigome, Ken; Chiba, Masamichi; Kai, Yukihiro; Sakai, Takeaki; Okuguchi, Fuminobu
CORPORATE SOURCE: Sch. Med., Tohoku Univ., Sendai, Japan
SOURCE: Tohoku Journal of Experimental Medicine (1977), 121(1), 27-32
CODEN: TJEMAO; ISSN: 0040-8727
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Thirty-one patients with subclin. **diabetes**, who showed diabetic or **impaired glucose tolerance** after treatment for **diabetes**, were investigated to clarify the abnormalities of insulin response in **diabetes** mellitus. These patients showed a delayed response of plasma insulin during oral glucose loading. In the **tolbutamide**-glucose test, in which glucose loading followed the i.v. **tolbutamide** injection at a 60-min interval, the insulin level at 90 min was significantly lowered in a group of 20 patients with subclin. **diabetes**. In the **tolbutamide**-glucagon test, in which 1 mg glucagon was injected 60 min after **tolbutamide** injection, the maximal level of plasma insulin was significantly decreased in a group of 10 subclin. diabetics, except for 1 patient. These results indicate that insulinogenesis and (or) release of insulin were decreased even in subclin. **diabetes**, suggesting that such a defect in islet function might be 1 of the abnormalities in primary **diabetes**.

L18 ANSWER 30 OF 31 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1975:168444 HCAPLUS
DOCUMENT NUMBER: 82:168444
TITLE: Endogenous and exogenous insulin responses in patients with cystic fibrosis
AUTHOR(S): Wilmshurst, Errol G.; Soeldner, J. Stuart; Holsclaw,

Douglas S.; Kaufmann, Robert L.; Shwachman, Harry; Aoki, Thomas T.; Gleason, Ray E.
CORPORATE SOURCE: Dep. Med., Peter Bent Brigham Hosp., Boston, MA, USA
SOURCE: Pediatrics (1975), 55(1), 75-82
CODEN: PEDIAU; ISSN: 0031-4005
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Eight male patients with cystic fibrosis, normal nutrition, normal phys. activity, relatively mild pulmonary disease, no evidence of liver disease, and no family history of **diabetes** mellitus underwent a series of carbohydrate tolerance tests in comparison with matched controls. The patients had **impaired glucose tolerance** and lower serum immunoreactive insulin levels during oral and intravenous glucose tolerance tests; serum insulin levels were also lower after intravenous administration of **tolbutamide** in the patients, but the redn. in blood glucose in each group was not signifiicantly different. During an intravenous insulin test, the decrease in blood glucose was the same for both groups, in spite of lower serum insulin levels in the patients with cystic fibrosis. The decrease in plasma free fatty acids was at least as great in the patients as in controls during the test procedures, while a decrease in plasma after intravenously administered insulin was seen only in the patients with cystic fibrosis. The carbohydrate intolerance of patients with cystic fibrosis apparently is due to an impaired insulin response to glucose, but this insulin deficiency is partly compensated by increased peripheral tissue sensitivity to insulin.

L18 ANSWER 31 OF 31 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1972:151843 HCAPLUS
DOCUMENT NUMBER: 76:151843
TITLE: Hepatic metabolic pathways and hormonal status in experimental nephrotic syndrome
AUTHOR(S): Shafir, Eleazar; Brenner, Talma; Gutman, Alisa; Orevi, Miriam; Diamant, Sophia; Mayer, Michael
CORPORATE SOURCE: Dep. Biochem., Hadassah Univ. Hosp., Jerusalem, Israel
SOURCE: Israel Journal of Medical Sciences (1972), 8(3), 271-84
CODEN: IJMDAI; ISSN: 0021-2180
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Incorporation of amino acid radioactivity into perfusate proteins and lipoproteins was detd. following ultracentrifugation. Nephrosis induced an increase in incorporation of amino acid label into the protein moiety of the very low- and the low-d. lipoproteins (<1.063). Incorporation into lipids was decreased. The label in albumin and globulin in the fraction with d. >1.21 from nephrotic liver perfusate was twice normal, whereas the label in lipids of this fraction was decreased. These results indicated that in the nephrotic condition the amino acids were poor precursors of lipid synthesis. Glucose given in the form of in vivo load was a good precursor of plasma lipids in nephrosis. The glucose tended to increase the liver lipid content. It was suggested that hyperlipogenesis occurred in nephrosis but it was not a prerequisite of nephrotic **hyperlipidemia**. The synthesis of a lipoprotein was a detg. factor. Hypoinsulinemia and decreased serum corticosterone levels were present in the exptl. nephrotic syndrome in rats assocd. with decreased glucose levels both in the fed and fasted state. Further, the hypoinsulinemia resulting from **impaired glucose tolerance** and the plasma insulin response after glucose load,

delayed insulin secretion after **tolbutamide** administration. The low serum insulin levels and insulin secretion capacity were consistent with decreased liver glycolysis as a result of decreased glucokinase, pyruvate kinase, and glucose-6-phosphate dehydrogenase activities.

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=> d que stat l22
L7             1 SEA FILE=REGISTRY ABB=ON  GLIMEPIRIDE/CN
L13         2188 SEA FILE=HCAPLUS ABB=ON  (IGT OR IFG OR ?IMPAIR?(W)(?GLUCOSE?(W
                 )?TOLERAN? OR ?FASTING?(W)?GLUCOSE?))
L14         6539 SEA FILE=HCAPLUS ABB=ON  (L7 OR ?NATEGLINID? OR ?REPAGLINID?
                 OR ?GLIMEPIRIDE? OR ?METFORMIN? OR ?TOLBUTAMID? OR ?GLICLAZID?
                 OR ?GLIPIZID?)
L17           46 SEA FILE=HCAPLUS ABB=ON  L13(L)L14
L18           31 SEA FILE=HCAPLUS ABB=ON  L17(L)(?DIABETES? OR ?DYSLIPIDEMIA?
                 OR ?HYPERLIPIDEMIA? OR ?HIGH?(W)?BLOOD?(W)?PRESSURE? OR
                 ?HYPERTENS? OR ?URICEMIA? OR ?ATHEROSCLER? OR ?ARTERIOSCLER?
                 OR ?RETINOPATH? OR ?NEPHROPATH?)
L19          180 SEA L18
L20           99 DUP REMOV L19 (81 DUPLICATES REMOVED)
L21           87 SEA L20(L)(?TREAT? OR ?THERAP? OR ?PREVENT? OR ?INHIBIT? OR
                 ?CONTROL?)
L22           15 SEA L21(L) ?METHOD?

=> d l22 ibib abs 1-15

L22  ANSWER 1 OF 15     MEDLINE
ACCESSION NUMBER:   2002716691     IN-PROCESS
DOCUMENT NUMBER:    22341191   PubMed ID: 12453951
TITLE:              Nateglinide improves early insulin secretion and controls
                    postprandial glucose excursions in a prediabetic
                    population.
AUTHOR:             Saloranta Carola; Guitard Christiane; Pecher Eckhard; De
                    Pablos-Velasco Pedro; Lahti Kaj; Brunel Patrick; Groop Leif
CORPORATE SOURCE:   Helsinki University Hospital, Department of Medicine,
                    Finland.
SOURCE:             DIABETES CARE, (2002 Dec) 25 (12) 2141-6.
                    Journal code: 7805975. ISSN: 0149-5992.
PUB. COUNTRY:       United States
DOCUMENT TYPE:      Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:           English
FILE SEGMENT:       IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE:         Entered STN: 20021218
                    Last Updated on STN: 20021218
AB   OBJECTIVE: The purpose of this study was to evaluate the metabolic
     effectiveness, safety, and tolerability of nateglinide in
     subjects with impaired glucose tolerance (
     IGT) and to identify a dose appropriate for use in a
     diabetes prevention study. RESEARCH DESIGN AND
     METHODS: This multicenter, double-blind, randomized,
     parallel-group, fixed-dose study of 8 weeks' duration was performed in a
     total of 288 subjects with IGT using a 2:2:2:1 randomization.
     Subjects received nateglinide (30, 60, and 120 mg) or placebo
     before each main meal. Metabolic effectiveness was assessed during a
     standardized meal challenge performed before and after the 8-week
     treatment. All adverse events (AEs) were recorded, and confirmed
     hypoglycemia was defined as symptoms accompanied by a self-monitoring of
     blood glucose measurement < or =3.3 mmol/l (plasma glucose < or =3.7
     mmol/l). RESULTS: Nateglinide elicited a dose-related increase
     of insulin and a decrease of glucose during standardized meal challenges,
     with the predominant effect on early insulin release, leading to a
     substantial reduction in peak plasma glucose levels. Nateglinide
     was well tolerated, and symptoms of hypoglycemia were the only
     treatment-emergent AEs. Confirmed hypoglycemia occurred in 28
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subjects receiving **nateglinide** (30 mg, 0 [0%]; 60 mg, 5 [6.6%]; 120 mg, 23 [26.7%]) and in 1 (2.3%) subject receiving placebo. CONCLUSIONS: **Nateglinide** was safe and effective in reducing postprandial hyperglycemia in subjects with **IGT**. Preprandial doses of 30 or 60 mg **nateglinide** would be appropriate to use for longer-term studies to determine whether a rapid-onset, rapidly reversible, insulinotropic agent can delay or **prevent** the development of type 2 **diabetes**.

L22 ANSWER 2 OF 15 MEDLINE
ACCESSION NUMBER: 2002169939 MEDLINE
DOCUMENT NUMBER: 21900894 PubMed ID: 11903417
TITLE: The NEPI antidiabetes study (NANSY). 1: short-term dose-effect relations of glimepiride in subjects with impaired fasting glucose.
AUTHOR: Lindblad U; Lindwall K; Sjostrand A; Ranstam J; Melander A
CORPORATE SOURCE: Skaraborg Institute, Skovde, Sweden. (The NEPI Antidiabetes Sstudy (NANSY)).
SOURCE: DIABETES, OBESITY & METABOLISM, (2001 Dec) 3 (6) 443-51. Journal code: 100883645. ISSN: 1462-8902.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(MULTICENTER STUDY)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200205
ENTRY DATE: Entered STN: 20020321
Last Updated on STN: 20020511
Entered Medline: 20020510

AB AIM: NANSY is a randomised, placebo-**controlled** Swedish-Norwegian study which aims to include 2 x 1112 male and female subjects with **impaired fasting glucose** (**IFG**), to assess whether conversion to type 2 **diabetes** can be delayed by addition of sulphonylurea to dietary regulation and increased exercise. This pilot study was conducted to find the optimum dose of **glimepiride** in NANSY. **METHODS**: In a double blind trial in primary care 25 **IFG** subjects were in random order exposed to single doses and one-week **treatments** with 0 (placebo), 0.5, 1.0 and 2.0 mg **glimepiride** once daily. The optimum dose was assessed by measuring blood glucose during oral 75 g glucose tolerance test (OGTT), comparing fasting blood glucose, and the area under the blood glucose curve (AUC), and by monitoring hypoglycaemic events. RESULTS: With single doses, there was a clear dose-response relationship for the reduction in AUC, with a statistically significant difference only between placebo (mean 1981, 95% confidence intervals (CI) 1883-2078) and 2 mg **glimepiride** (mean 1763, 95% CI 1665-1861). However, following 1-week **treatments**, the only significant difference was between placebo (mean 1934, 95% CI 1856-2012) and 1 mg **glimepiride** (mean 1714, 95% CI 1637-1792). Correspondingly, the only statistically significant difference in fasting blood glucose day 7 was between placebo (5.87 mmol/l, 95% CI 5.68-6.05 mmol/l) and 1 mg **glimepiride** (5.42 mmol/l, 95% CI 5.21-5.62 mmol/l). Chemical hypoglycaemia was common but hypoglycaemic symptoms were rare and similar between the active doses, and easily countered by the subjects. CONCLUSIONS: The sulphonylurea dose-effect curve may be bell-shaped, perhaps due to down regulation of sulphonylurea receptors during chronic exposure. Alternatively, the

finding could be a rebound phenomenon, secondary to preceding hypoglycaemia. The optimum dose for NANSY was found to be 1 mg **glimepiride**.

L22 ANSWER 3 OF 15 MEDLINE
ACCESSION NUMBER: 2001681670 MEDLINE
DOCUMENT NUMBER: 21584768 PubMed ID: 11727406
TITLE: Insulin therapy in type 2 diabetes.
AUTHOR: Mudaliar S; Edelman S V
CORPORATE SOURCE: Section of Diabetes/Metabolism, VA San Diego HealthCare System, Department of Medicine, University of California at San Diego, San Diego, California, USA.
SOURCE: ENDOCRINOLOGY AND METABOLISM CLINICS OF NORTH AMERICA, (2001 Dec) 30 (4) 935-82. Ref: 71
Journal code: 8800104. ISSN: 0889-8529.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200204
ENTRY DATE: Entered STN: 20011203
Last Updated on STN: 20020501
Entered Medline: 20020430

AB Type 2 **diabetes** is a common disorder often accompanied by numerous metabolic abnormalities leading to a high risk of cardiovascular morbidity and mortality. Results from the UKPDS have confirmed that intensive glucose **control** delays the onset and retards the progression of microvascular disease and possibly of macrovascular disease in patients with type 2 **diabetes**. In the early stages of the disease, insulin resistance plays a major role in the development of hyperglycemia and other metabolic abnormalities, and patients with type 2 **diabetes** often benefit from measures to improve insulin sensitivity such as weight loss, dietary changes, and exercise. Later, the use of oral insulin secretagogues and insulin sensitizers as **monotherapy** and in combination helps maintain glycemia for varying periods of time. Ultimately, because of the progressive nature of the disease and the progressive decline in pancreatic beta-cell function, insulin **therapy** is almost always obligatory to achieve optimal glycemic goals. Not all patients are candidates for aggressive insulin management; therefore, the goals of **therapy** should be modified, especially in elderly individuals and those with co-morbid conditions. Candidates for intensive management should be motivated, compliant, and educable, without other major medical conditions and physical limitations that would preclude accurate and reliable HGM and insulin administration. In selected patients, combination **therapy** with insulin and oral antidiabetic medications can be an effective **method** for normalizing glycemia without the need for rigorous multiple-injection regimens. The patients for whom combination **therapy** is most commonly successful are those who do not achieve adequate glycemic **control** using daytime oral agents but who still show some evidence of responsiveness to the medications. Bedtime intermediate-acting or predinner premixed intermediate- and rapid-acting insulin is administered and progressively increased until the FPG concentration is normalized. If combination **therapy** is not successful, a split-mixed regimen of intermediate- and rapid-acting insulin equally divided between the prebreakfast and pre-dinner periods is advised for oese patients, and more

intensive regimens are advised for thin patients. Insulin **therapy** is invariably associated with weight gain and hypoglycemia. The use of **metformin** or glitazones in combination with insulin has been demonstrated to have insulin-sparing properties. Also, **metformin** use may ameliorate weight gain. The use of continuous subcutaneous insulin infusion pumps can be particularly beneficial in **treating** patients with type 2 **diabetes** mellitus who do not respond satisfactorily to more conventional **treatment** strategies. Intraperitoneal insulin delivery systems hold considerable promise in type 2 **diabetes** because of their more physiologic delivery of insulin and their ability to **inhibit** hepatic glucose production selectively, with less peripheral insulinemia than with subcutaneous insulin injections. Newer insulin analogues such as the rapidly acting Lispro insulin and the peakless, long-acting glargine insulin are increasingly being used because of their unique physiologic pharmacokinetics. New developments such as inhaled and buccal insulin preparations will also make it easier for many patients to initiate and maintain a proper insulin regimen. Finally, a new generation of gut peptides such as amylin and GLP-1 will add a new dimension to glycemic **control** through modification of nutrient delivery and other mechanisms; however, the ultimate goal in the management of type 2 **diabetes** is the primary **prevention** of the disease. The **Diabetes Prevention** Program (DPP) sponsored by the National Institutes of Health has currently randomly assigned more than 3000 persons with **impaired glucose tolerance** and at high risk of developing **diabetes** into three **treatment** arms: **metformin** arm, an intensive lifestyle-modification arm, and a placebo arm. The study will conclude in 2002 after all participants have been followed for 3 to 6 years.

L22 ANSWER 4 OF 15 MEDLINE
ACCESSION NUMBER: 2001503752 MEDLINE
DOCUMENT NUMBER: 21437458 PubMed ID: 11553189
TITLE: Metabolic effects of metformin in patients with impaired glucose tolerance.
AUTHOR: Lehtovirta M; Forsen B; Gullstrom M; Haggblom M; Eriksson J G; Taskinen M R; Groop L
CORPORATE SOURCE: Department of Medicine, Helsinki University Hospital, Helsinki, Finland.
SOURCE: DIABETIC MEDICINE, (2001 Jul) 18 (7) 578-83.
Journal code: 8500858. ISSN: 0742-3071.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: (CLINICAL TRIAL)
(CONTROLLED CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200112
ENTRY DATE: Entered STN: 20010913
Last Updated on STN: 20020122
Entered Medline: 20011220

AB AIMS: To assess the effect of **metformin** on insulin sensitivity, glucose tolerance and components of the metabolic syndrome in patients with **impaired glucose tolerance** (**IGT**). **METHODS**: Forty first-degree relatives of patients with Type 2 **diabetes** fulfilling WHO criteria for **IGT** and participating in the Botnia study in Finland were randomized to **treatment** with either **metformin** 500 mg b.i.d. or placebo

for 6 months. An oral glucose tolerance test (OGTT) and a euglycaemic hyperinsulinaemic clamp in combination with indirect calorimetry was performed at 0 and 6 months. The patients were followed after stopping **treatment** for another 6 months in an open trial and a repeat OGTT was performed at 12 months. RESULTS: **Metformin treatment** resulted in a 20% improvement in insulin-stimulated glucose metabolism (from 28.7 +/- 13 to 34.4 +/- 10.7 micromol/kg fat-free mass (FFM)/min) compared with placebo (P = 0.01), which was primarily due to an increase in glucose oxidation (from 16.6 +/- 3.6 to 19.1 +/- 4.4 micromol/kg FFM; P = 0.03) These changes were associated with a minimal improvement in glucose tolerance, which was maintained after 12 months. CONCLUSIONS: **Metformin** improves insulin sensitivity in subjects with **IGT** primarily by reversal of the glucose fatty acid cycle. Obviously large multicentre studies are needed to establish whether these effects are sufficient to **prevent** progression to manifest Type 2 **diabetes** and associated cardiovascular morbidity and mortality. Diabet. Med. 18, 578-583 (2001)

L22 ANSWER 5 OF 15 MEDLINE
ACCESSION NUMBER: 2001426603 MEDLINE
DOCUMENT NUMBER: 21366817 PubMed ID: 11475232
TITLE: [Can type 2 diabetes be prevented?].
Kan type 2-diabetes forebygges?.
AUTHOR: Berg T J
CORPORATE SOURCE: Aker Diabetes Forskningssenter Aker sykehus 0514 Oslo..
t.j.berg@ioks.uio.no
SOURCE: TIDSSKRIFT FOR DEN NORSKE LAEGEFORENING, (2000 Aug 30) 120 (20) 2430-3.
Journal code: 0413423. ISSN: 0029-2001.
PUB. COUNTRY: Norway
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Norwegian
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200108
ENTRY DATE: Entered STN: 20010813
Last Updated on STN: 20010813
Entered Medline: 20010809

AB BACKGROUND: The prevalence of type 2 **diabetes** among Norwegian men increased from 2.6% to 3.3% from 1986 to 1997. The most important environmental risk factors for type 2 **diabetes** are obesity and reduced physical activity. Genetic factors are also strongly involved. Biochemical risk factors are **impaired glucose tolerance** and decreased insulin response. MATERIAL AND **METHODS**: Only a few small studies have investigated the possibility of primary **prevention** of type 2 **diabetes**. RESULTS: In a six-year intervention study on persons with **impaired glucose tolerance** in China, diet and/or increased physical activity reduced the risk of type 2 **diabetes** by 30 to 50%. Similar results were found in a study from Sweden. No drug is shown to **prevent** type 2 **diabetes**. Possible candidates are **metformin** and thiazolidinediones which increase insulin sensitivity, and pancreatic lipase **inhibitors** which reduce the absorption of fat from the gut. Three large, randomised, prospective studies are investigating whether life style intervention or medication can **prevent** the disease. The results of these studies will be available in about five years. INTERPRETATION: Present evidence clearly indicates that increased physical activity and diet can **prevent** the development of type 2 **diabetes**.

L22 ANSWER 6 OF 15 MEDLINE
ACCESSION NUMBER: 2001303127 MEDLINE
DOCUMENT NUMBER: 20540820 PubMed ID: 11092283
TITLE: The Diabetes Prevention Program: baseline characteristics of the randomized cohort. The Diabetes Prevention Program Research Group.
AUTHOR: Anonymous
SOURCE: DIABETES CARE, (2000 Nov) 23 (11) 1619-29.
Journal code: 7805975. ISSN: 0149-5992.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(MULTICENTER STUDY)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200105
ENTRY DATE: Entered STN: 20010604
Last Updated on STN: 20010604
Entered Medline: 20010531

AB OBJECTIVE: The **Diabetes Prevention** Program (DPP) is a 27-center randomized clinical trial designed to evaluate the safety and efficacy of interventions that may delay or **prevent** development of **diabetes** in people at increased risk for type 2 **diabetes**. RESEARCH DESIGN AND **METHODS**: Eligibility requirements were age > or = 25 years, BMI > or = 24 kg/m2 (> or = 22 kg/m2 for Asian-Americans), and **impaired glucose tolerance** plus a fasting plasma glucose of 5.3-6.9 mmol/l (or < or = 6.9 mmol for American Indians). Randomization of participants into the DPP over 2.7 years ended in June 1999. Baseline data for the three **treatment** groups--intensive lifestyle modification, standard care plus **metformin**, and standard care plus placebo--are presented for the 3,234 participants who have been randomized. RESULTS: Of all participants, 55% were Caucasian, 20% were African-American, 16% were Hispanic, 5% were American Indian, and 4% were Asian-American. Their average age at entry was 51 +/- 10.7 years (mean +/- SD), and 67.7% were women. Moreover, 16% were < 40 years of age, and 20% were > or = 60 years of age. Of the women, 48% were postmenopausal. Men and women had similar frequencies of history of hypercholesterolemia (37 and 33%, respectively) or **hypertension** (29 and 26%, respectively). On the basis of fasting lipid determinations, 54% of men and 40% of women fit National Cholesterol Education Program criteria for abnormal lipid profiles. More men than women were current or former cigarette smokers or had a history of coronary heart disease. Furthermore, 66% of men and 71% of women had a first-degree relative with **diabetes**. Overall, BMI averaged 34.0 +/- 6.7 kg/m2 at baseline with 57% of the men and 73% of women having a BMI > or = 30 kg/m2. Average fasting plasma glucose (6.0 +/- 0.5 mmol/l) and HbA1c (5.9 +/- 0.5%) in men were comparable with values in women (5.9 +/- 0.4 mmol/l and 5.9 +/- 0.5%, respectively). CONCLUSIONS: The DPP has successfully randomized a large cohort of participants with a wide distribution of age, obesity, and ethnic and racial backgrounds who are at high risk for developing type 2 **diabetes**. The study will examine the effects of interventions on the development of **diabetes**.

L22 ANSWER 7 OF 15 MEDLINE
ACCESSION NUMBER: 2000471789 MEDLINE
DOCUMENT NUMBER: 20324687 PubMed ID: 10868835

TITLE: Reduced beta-cell compensation to the insulin resistance associated with obesity in members of caucasian familial type 2 diabetic kindreds.
AUTHOR: Elbein S C; Wegner K; Kahn S E
CORPORATE SOURCE: Endocrinology Section, Central Arkansas Veterans Healthcare System, University of Arkansas for Medical Sciences, Little Rock, USA.. elbeinstevenc@exchange.uams.edu
CONTRACT NUMBER: DK17047 (NIDDK)
DK39311 (NIDDK)
SOURCE: DIABETES CARE, (2000 Feb) 23 (2) 221-7.
Journal code: 7805975. ISSN: 0149-5992.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200010
ENTRY DATE: Entered STN: 20001012
Last Updated on STN: 20001012
Entered Medline: 20001002

AB OBJECTIVE: Both obesity and a family history of **diabetes** reduce insulin sensitivity, but the impact of obesity on insulin secretion among individuals predisposed to **diabetes** is uncertain. We used a pedigree-based approach to test the hypothesis that beta-cell compensation to the insulin resistance associated with obesity is defective among individuals predisposed to **diabetes** by virtue of a strong family history of type 2 **diabetes** before the development of **diabetes** or glucose intolerance. RESEARCH DESIGN AND **METHODS**: A total of 126 members of 26 families ascertained for at least a sib pair with type 2 **diabetes** with onset before age 65 years underwent a **tolbutamide**-modified frequently sampled intravenous glucose tolerance test (FSIGT). Family members included 26 individuals with **impaired glucose tolerance** and 100 individuals with normal glucose tolerance (NGT). The acute insulin response to glucose (AIRglucose) was determined and insulin sensitivity (S(I)) estimated by minimal model analysis of FSIGT data. The beta-cell compensation for insulin sensitivity was estimated from the disposition index (DI), calculated as the product of S(I) and AIRglucose. Obesity was measured by BMI. RESULTS: Among all individuals, BMI was a significant predictor of both S(I) and AIRglucose, as expected. However, BMI also significantly predicted DI (P = 0.002) after correcting for age, sex, family membership, and glucose tolerance status. The relationship of BMI and DI was confirmed in 85 individuals with NGT who were aged <45 (P = 0.002) but not in 91 unrelated **control** individuals without a family history of **diabetes**. When normoglycemic individuals aged <45 were separated into three classes by BMI (< or =27, 27-30, >30), S(I) decreased progressively and significantly with obesity whereas AIRglucose rose significantly from lean to most obese classes. In contrast to the expectation of complete beta-cell compensation with obesity D1 fell significantly (P = 0.004) among obese family members. This relationship was not observed in **control** subjects. CONCLUSIONS: Individuals with a genetic predisposition to **diabetes** show a reduced beta-cell compensatory response to the reduced insulin sensitivity associated with obesity. We propose that this impaired compensation may be one manifestation of the underlying genetic defect in susceptible individuals. This finding helps explain the multiplicative effects of family history and obesity on risk of type 2 **diabetes**.

L22 ANSWER 8 OF 15 MEDLINE

ACCESSION NUMBER: 1999318279 MEDLINE
DOCUMENT NUMBER: 99318279 PubMed ID: 10391395
TITLE: Effect of metformin on patients with impaired glucose tolerance.
AUTHOR: Li C L; Pan C Y; Lu J M; Zhu Y; Wang J H; Deng X X; Xia F C; Wang H Z; Wang H Y
CORPORATE SOURCE: Department of Endocrinology, Chinese PLA General Hospital, Beijing.. Licl@plagh.com.cn
SOURCE: DIABETIC MEDICINE, (1999 Jun) 16 (6) 477-81.
Journal code: 8500858. ISSN: 0742-3071.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199908
ENTRY DATE: Entered STN: 19990827
Last Updated on STN: 19990827
Entered Medline: 19990819

AB AIMS: To evaluate the effect of **metformin** on glucose metabolism, insulin sensitivity and rate of conversion **diabetes** in people with **impaired glucose tolerance** (**IGT**). **METHODS**: Seventy subjects with **IGT** were randomized under double-blind conditions to receive either placebo (n = 37) or **metformin** (n = 33) at a dosage of 250 mg three times daily for a duration of 12 months. Glycaemic **control**, plasma insulin and other biochemical indexes were assessed before and after 3, 6 and 12 months. RESULT: At 12 months the conversion rate to **diabetes** was 16.2% in the placebo group compared to 3.0% for the **metformin** group (P = 0.011). Of subjects **treated** with **metformin** for 12 months, 84.9% became normoglycaemic compared to 51.4% of those receiving the placebo. Significant improvements in fasting glucose, glucose tolerance and insulin sensitivity were found at 12 months and at intermediate clinic assessments. CONCLUSIONS: **Metformin** can improve glucose metabolism in **IGT** patients and may be a **treatment** option in their management of **IGT** subjects.

L22 ANSWER 9 OF 15 MEDLINE
ACCESSION NUMBER: 94228685 MEDLINE
DOCUMENT NUMBER: 94228685 PubMed ID: 8174247
TITLE: Immunoradiometric assay of human intact proinsulin applied to patients with type 2 diabetes, impaired glucose tolerance, and hyperandrogenism.
AUTHOR: Chevenne D; Ruiz J; Lohmann L; Laudat A; Leblanc H; Gray I P; Passa P; Porquet D
CORPORATE SOURCE: Hopital Robert Debre, Laboratoire de Biochimie-Hormonologie, Paris, France.
SOURCE: CLINICAL CHEMISTRY, (1994 May) 40 (5) 754-7.
Journal code: 9421549. ISSN: 0009-9147.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199406
ENTRY DATE: Entered STN: 19940620
Last Updated on STN: 19940620
Entered Medline: 19940608

AB We describe an immunoradiometric assay for human intact proinsulin in serum. In this **method**, one monoclonal antibody, coated onto polyacrylamide beads, cross-reacts with proinsulins and insulin. A sandwich is formed with intact proinsulin, split (65-66) proinsulin, and des (64-65) proinsulin binding with an 125I-labeled monoclonal antibody specific for an epitope at the intact B-C junction of proinsulin. Because split (65-66) and des (64-65) proinsulin concentrations are very low in serum, this assay essentially measures intact proinsulin. When we used 1-mL serum samples, the mean detection limit was 0.4 pmol/L. Mean proinsulin concentrations (pmol/L) were 3.4 (range 1-9.1) in healthy fasting subjects, 28.5 (9.7-101) in patients with type 2 **diabetes** (**treated** with **metformin** and sulfonylureas), 5.0 (1.6-9.3) in women with hyperandrogenism and normal insulinemia, 10.3 (2.6-36) in women with hyperandrogenism and hyperinsulinemia, and 8.5 (4.8-21.3) in patients with **impaired glucose tolerance**.

L22 ANSWER 10 OF 15 WPIDS (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 2003-040576 [03] WPIDS
DOC. NO. CPI: C2003-009562
TITLE: New melanin-concentrating hormone antagonists useful for e.g. treating eating disorders, metabolic disorders or diabetes.
DERWENT CLASS: B02 B03
INVENTOR(S): CHAN, T; CLADER, J W; JOSIEN, H B; PALANI, A
PATENT ASSIGNEE(S): (SCHE) SCHERING CORP
COUNTRY COUNT: 96
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2002076947	A1	20021003	(200303)*	EN	129

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CZ DE DK DM DZ EC EE ES FI GB GD GE HR HU ID IL IN IS JP KG KR KZ LC LK LR LT LU LV MA MD MG MK MN MX MZ NO NZ PH PL PT RO RU SE SG SI SK SL TJ TM TN TR TT TZ UA UZ VN YU ZA ZM

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2002076947	A1	WO 2002-US8338	20020320

PRIORITY APPLN. INFO: US 2001-277584P 20010321
AN 2003-040576 [03] WPIDS
AB WO 200276947 A UPAB: 20030113
NOVELTY - Melanin-concentrating hormone (MCH) antagonists (I), their salts, solvates or prodrugs are new.
DETAILED DESCRIPTION - Melanin-concentrating hormone (MCH) antagonists of formula (I), their salts, solvates or prodrugs are new;
m and n = 0 - 3;
X1 = CH, N or C-(1-3C)alkyl;
X2 = NR5, CH2, O, S, SO, SO2, (CH-(1-6C)alkyl) or CH-(CH2O-(1-3C)alkyl);
X3 = O or NR6;

X4 = single bond, O, N, NH or NR7;
Ar = (hetero)arylene;
R = R4-phenyl, R4-pyridyl, R4-pyridyl-N-oxide, R4-pyrazyl or R4-pyrimidyl;
R1 = H or 1-3C alkyl;
R2 = alkyl, optionally substituted arylalkyl, cycloalkyl, cycloalkylalkyl, R8-phenyl, R8-pyridiyl or R8-pyridyl-N-oxide;
R3 = H, OH, -O(1-3C)alkyl or optionally halo substituted 1-3C alkyl;
R4 and R8 = 0 - 3 group selected from H, 1-6C alkyl, 3-7C cycloalkyl, halo, -CN, 1-6C alkoxy, -CF3, -OCF3, -CONH2, -CONH(1-6C)alkyl, CON(1-6C)alkyl(1-6C) alkyl, -NH2, -NHC(O)(1-6C)alkyl, -NHC(O)NH(1-6C)alkyl, -NHC(O)N((1-6C)alkyl)((1-6C)alkyl), -NHSO2(1-6C)alkyl, -S(1-6C)alkyl, -SO(1-6C)alkyl, -SO2(1-6C)alkyl, -SO2NH(1-6C)alkyl, -O(1-3C)alkyleneO- or NO2;
R4+R4 or (R8+R8) = methylenedioxy, propylenedioxy or ethylenedioxy group;
R5 = 1-6C alkyl, 3-7C cycloalkyl, (3-7C)cycloalkyl(1-6C)alkyl, (1-6C)alkylene(1-6C)alkoxy, alkoxycarbonyl, aryl, heterocycloalkyl, heteroaryl, aralkyl, (1-6C)alkylbenzimidazolyl, heteroaralkyl, C(O)NH(1-3C)alkylene N(R9)2 or -SO2-(1-6C)alkyl (all optionally halo substituted), H, SO2NH2, -SO2NHalkyl, -SO2N(alkyl)2, pyrolidin-1-sulfonyl or piperidin-1-sulfonyl;
R6 and R7 = H or optionally halo substituted (1-3C)alkyl;
R6+R7 = 4 - 7 membered ring;
R9 = H, 1-6C alkyl, 3-7C cycloalkyl, 3-7C cycloalkylmethyl or (hetero)aralkyl; and
N(R9)2 = pyrrolidine, piperazine or piperidine.
Provided that when X4 is N, R2 and X4 can join together to form a heterocycloalkyl group such as piperidine, pyrrolidine, morpholine, piperazine, thiomorpholine, R4-benzosubstituted-(1H)-indole, R4-benzosubstituted-(1H)-2,3-dihydroindole, where N of X4 is heteroatom of heterocyclic group, which can further be optionally substituted with one or more alkyl, aryl, aralkyl, or cycloalkylalkyl groups.
INDEPENDENT CLAIMS are also included for:
(1) a pharmaceutical composition comprising a compound that contains two components and carrier. The first component is a compound of formula (I), its prodrug or salt. The second component is an antiobesity and/or anorectic agent such as a beta -agonist, a thyromimetic agent, anorectic agent or NPY antagonist;
(2) a pharmaceutical composition comprising a compound that contains two component and carrier. The first compound is of formula (I), its prodrug or salt. The second compound is aldose reductase **inhibitor**, glycogen phosphorylase **inhibitor**, a sorbitol dehydrogenase **inhibitor**, a protein tyrosine phosphatase 1B **inhibitor**, a dipeptidyl protease **inhibitor**, insulin (including orally bioavailable insulin preparations), an insulin mimetic, **metformin**, acarbose, a PPAR-gamma ligand such as troglitazone, rosaglitazone, pioglitazone, GW-1929, a sulfonylurea, glipazide, glyburide or chlorpropamide; and
(3) a **method** for preparing a pharmaceutical composition containing (I).
ACTIVITY - Anorectic; Antidiabetic; Hypotensive; Cardiant; Cytostatic; Antilipemic; Litholytic; Hepatotropic.
MECHANISM OF ACTION - Melanin-concentrating hormone (MCH) antagonist.
Test details are given, but no specific results are given.
USE - For the **treatment** of metabolic disorder, an eating disorder e.g. hyperphagia or **diabetes** e.g. obesity. The other disorders are type II **diabetes**, insulin resistance,

hyperlipidemia and **hypertension** (all claimed), sleep apnea, certain cancers, gall stones, cardiovascular disease and **impaired glucose tolerance.**
Dwg.0/0

L22 ANSWER 11 OF 15 WPIDS (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 2002-444013 [47] WPIDS
DOC. NO. CPI: C2002-126369
TITLE: New benzopyrancarboxylic acid derivatives, useful for treating e.g. cachexia, non-insulin dependent diabetes mellitus, hyperglycemia, obesity, dyslipidemia, hypercholesterolemia or atherosclerosis.
DERWENT CLASS: B02
INVENTOR(S): BOUERES, J K; DESAI, R C; KOYAMA, H; MILLER, D J; SAHOO, S P
PATENT ASSIGNEE(S): (BOUE-I) BOUERES J K; (DESA-I) DESAI R C; (KOYA-I) KOYAMA H; (MILL-I) MILLER D J; (SAHO-I) SAHOO S P; (MERI) MERCK & CO INC
COUNTRY COUNT: 96
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2002026729	A2	20020404	(200247)*	EN	87

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PH PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW

US 2002082292 A1 20020627 (200249)
AU 2001092874 A 20020408 (200252)

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2002026729 A2		WO 2001-US29456	20010921
US 2002082292 A1	Provisional	US 2000-235708P	20000927
	Provisional	US 2000-244697P	20001031
		US 2001-961841	20010924
AU 2001092874 A		AU 2001-92874	20010921

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2001092874 A	Based on	WO 200226729

PRIORITY APPLN. INFO: US 2000-244697P 20001031; US 2000-235708P 20000927; US 2001-961841 20010924
AN 2002-444013 [47] WPIDS
AB WO 200226729 A UPAB: 20020725
NOVELTY - Benzopyran-carboxylic acid derivatives and their salts and prodrugs are new.
DETAILED DESCRIPTION - Benzopyran-carboxylic acid derivatives of formula (I) and their salts and prodrugs are new:
Z' = CH2 or CO;

R1, R2, R3, R5, R6, R7, R8, R9, R10 = e.g. H, OH, optionally substituted, optionally unsaturated alkyl or aryl;
R4 = e.g. aryloxy; and
X, Y = e.g. O, S, SO, SO2, CH2 or optionally substituted NH.
Full definitions are given in the DEFINITIONS (Full Definitions and Preferred Definitions) section. INDEPENDENT CLAIMS are included for:
(1) Compositions comprising (I) and a **therapeutic** agent (as below);
(2) **Method** for disease where insulin resistance is a component, comprises administration of (I) and a **theraputic** agent:
(a) insulin sensitizers:
(i) peroxisome proliferator acitvated receptor- gamma (PPAR gamma) agonists, e.g. giltazones;
(ii) biguanides, e.g. **metformin** or phenformin;
(iii) protein tyrosine phosphatase-1B; and
(iv) dipeptidyl peptide IV **inhibitors**;
(b) insulin or insulin mimetics;
(c) sulfonylureas, e.g. **tolbutamide** or **glipizide**;
(d) alpha -glucosaidase **inhibitors**;
(e) cholesterol lowering agents;
(i) HMG-CoA reductase **inhibitors**;
(ii) sequestrants, e.g. cholestyramine or colestipol;
(iii) nicotinyl alcohol;
(iv) PPAR alpha agonists;
(v) PPAR alpha / gamma dual agonists;
(vi) **inhibitors** of cholesterol absorption, ezetimibe;
(vii) acyl CoA, cholesterol acetyl transferase **inhibitors**, e.g. avasimibe; and
(viii) anti-oxidants, e.g. probucol;
(f) PPAR delta agonists;
(g) antiobesity compounds, e.g. fenfluramine, dexfenfluramine, phenterminw, sibutramine, mazindol, orlistat, lipase **inhibitors**, neuropeptide Y5 **inhibitors** or beta -3 adrenergic receptor agonists;
(h) ileal bile acid transporter **inhibitor**; and
(i) inflammatory agent.
ACTIVITY - Immunomodulator; Antidiabetic; Anorectic; Antilipemic; Antiarteriosclerotic; Vasotropic; Antiinflammatory; Antiulcer; Cytostatic; Nootropic; Neuroprotective; Antipsoriatic; Antiseborrheic; Dermatological; Hypotensive.
No biological data available.
MECHANISM OF ACTION - PPAR alpha agonist; PPAR gamma agonist.
No biological data available.
USE - (I) are useful for treating cachexia, non-insulin dependent diabetes mellitus, hyperglycemia, impaired glucose tolerance, insulin resistance, obesity, lipid disorders, dyslipidemia, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, low HDL levels, high LDL levels, atherosclerosis, vascular restenosis, irritable bowel syndrome, inflammatory bowel disease, Crohn's disease, ulcerative colitis, inflammatory conditions, pancreatitis, abdominal obesity, neurodegenerative disease, retinopathy, neoplastic conditions, adipose cell tumors, adipose cell carcinomas, prostate cancer, gastric cancer, breast cancer, bladder cancer, colon cancer, angiogenesis, Alzheimer's disease, psoriasis, acne vulgaris, skin diseases modulated by PPAR, high blood pressure, syndrome X and ovarian hyperandrogenism.
Dwg.0/0

L22 ANSWER 12 OF 15 WPIDS (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 2002-351273 [38] WPIDS
CROSS REFERENCE: 2001-520159 [57]
DOC. NO. CPI: C2002-099679
TITLE: Treating conditions included within Coronary Heart Disease Risk Factor (CHDRF) syndrome comprises administering a composition comprising an opioidergic agent and an insulin secretagogue, e.g. hydrocodone and glipizide.
DERWENT CLASS: B05
INVENTOR(S): CLEMENS, A H
PATENT ASSIGNEE(S): (CPDC-N) CPD LLC
COUNTRY COUNT: 100
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
US 2002045636	A1	20020418	(200238)*		5
WO 2002100390	A2	20021219	(200301)	EN	

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 2002045636	A1 CIP of	US 2000-639061	20000815
		US 2001-878834	20010611
WO 2002100390	A2	WO 2002-US18863	20020606

FILING DETAILS:

PATENT NO	KIND	PATENT NO
US 2002045636	A1 CIP of	US 6262062

PRIORITY APPLN. INFO: US 2001-878834 20010611; US 2000-639061 20000815
AN 2002-351273 [38] WPIDS
CR 2001-520159 [57]
AB US2002045636 A UPAB: 20030101
NOVELTY - **Methods** (A)-(C) of **treating** a human suffering from one or more conditions included within Coronary Heart Disease Risk Factor (CHDRF) syndrome comprises administering a drug composition comprising an opioidergic agent (I) and an insulin secretagogue (II).
ACTIVITY - Cardiant; antidiabetic; anorectic; antilipemic; hepatotropic.
USE - The condition included within the CHDRF Syndrome is Insulin Resistance (IR), Beta-Cell Dysfunction, **Impaired Glucose Tolerance** (**IGT**), Type 2 **Diabetes**, overweight, obesity and **dyslipidemia** (all claimed).
ADVANTAGE - The combination of (I) and (II) provides an improved

method of **treating** CHDRF compared to **methods** described in e.g. US5878750 and US6026817. The **method** **treats** early morning increase in gluconeogenesis and increased glucose production which, in the presence of relatively impaired insulin secretion, results in elevated fasting glucose levels. The **method** restores the physiologic acute, first phase insulin release. Administering (I) in combination with (II) confers a more glucose dependent, bi-phasic insulin release pattern and significantly reduces the likelihood of producing hypoglycemia. The **method** also provides an improved first pass insulinization of the liver, resulting in a restoration of enzyme functions involved in hepatic fuel processing, including carbohydrate oxidation and storage.

DESCRIPTION OF DRAWING(S) - The figure is a graph showing the daily blood glucose profile of a 72-year old subject afflicted with type 2 **diabetes** and dislipidemia after **treatment** with an opioidergic drug composition comprising **glipizide**, in combination with an insulin secretagogue, hydrocodone. The blood glucose (BG) of the subject was measured in mg/dl over several time intervals measured in hours (h).

Dwg.1/1

L22 ANSWER 13 OF 15 WPIDS (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 2002-291951 [33] WPIDS
CROSS REFERENCE: 2002-666913 [71]
DOC. NO. CPI: C2002-085735
TITLE: Use of a selective cGMP phosphodiesterase-5 inhibitor for treatment of insulin resistance syndrome including dyslipidemia, hypertension, type II diabetes mellitus, impaired glucose tolerance, atherosclerosis or truncal obesity.
DERWENT CLASS: B02
INVENTOR(S): FRYBURG, D A; GIBBS, E M; KOPPIKER, N P
PATENT ASSIGNEE(S): (FRYB-I) FRYBURG D A; (GIBB-I) GIBBS E M; (KOPP-I) KOPPIKER N P; (PFIZ) PFIZER INC; (PFIZ) PFIZER LTD
COUNTRY COUNT: 96
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2002013798	A2	20020221	(200233)*	EN	60
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW					
AU 2001076607	A	20020225	(200245)		
US 2002143015	A1	20021003	(200267)		
US 2002165237	A1	20021107	(200275)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2002013798	A2	WO 2001-IB1428	20010806
AU 2001076607	A	AU 2001-76607	20010806
US 2002143015	A1 Provisional	US 2001-266083P	20010202
		US 2002-60788	20020130

US 2002165237 A1	Provisional	US 2000-224928P	20000811
	Provisional	US 2000-256431P	20001218
	Provisional	US 2001-266083P	20010202
	Provisional	US 2001-292506P	20010521
		US 2001-927525	20010810

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2001076607 A	Based on	WO 200213798

PRIORITY APPLN. INFO: GB 2001-17134 20010713; US 2000-224928P 20000811; GB 2000-30649 20001215; US 2001-266083P 20010202; GB 2001-6465 20010315; GB 2001-6468 20010315

AN 2002-291951 [33] WPIDS

CR 2002-666913 [71]

AB WO 200213798 A UPAB: 20021120

NOVELTY - Use of a selective cyclic guanosine monophosphate (cGMP) phosphodiesterase-5 (PDE-5) **inhibitor** (I) for curative, palliative or prophylactic **treatment** of insulin resistance syndrome (i.e. existence of 2 or more of **dyslipidemia**, **hypertension**, type II **diabetes** mellitus, **impaired glucose tolerance** (**IGT**), family history of **diabetes**, **hyperuricemia** and/or gout, a procoagulant state, **atherosclerosis** or truncal obesity, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for:

(1) use of sildenafil for the preparation of a medicament for curative, palliative or prophylactic **treatment** of insulin resistance syndrome in a patient having **dyslipidemia**, **hypertension**, type II **diabetes** mellitus, **impaired glucose tolerance** (**IGT**) or family history of **diabetes** and truncal obesity;

(2) use of sildenafil in combination with other agents for the preparation of a medicament for curative, palliative or prophylactic **treatment** of insulin resistance syndrome in a patient having **dyslipidemia**, **hypertension**, type II **diabetes** mellitus, **impaired glucose tolerance** (**IGT**) or family history of **diabetes** and truncal obesity;

(3) a **method** of **treating** insulin resistance syndrome comprising administration of (I) or its salt, solvate or composition;

(4) a **method** of **treating** insulin resistance syndrome comprising administration of (I) in combination with 1 or more protein kinase **inhibitors**, activators or AMP-activated protein kinases, weight loss agents, insulin, peroxisome proliferator-activated receptor (PPAR)- alpha agonists, PPAR- alpha /PPAR- gamma agonists, sorbitol dehydrogenase **inhibitors**, aldose reductase **inhibitors**, insulin sensitizing agents and/or hypoglycemic agents;

(5) use of a selective pyrazolopyrimidinone cGMP PDE-5 **inhibitor** for the **treatment** of **IGT**; and

(6) a **method** of **treating** insulin resistance syndrome comprising administration of (I), preferably sildenafil, in combination with 1 or more weight loss agents, sulfonylureas, insulin, Rezulin, Avandia, Actos, **Glipizide**, **Metformin**, Acarbose, rosiglitazone, pioglitazone, farglitazar, LY333531, CS011, PPAR-

alpha agonists and/or CP-470711.

ACTIVITY - Antidiabetic; Antilipemic; Anorectic; **Antiarteriosclerotic**; Uropathic; Hypotensive; Antigout; Vasotropic; Anticoagulant.

In a clinical trial in adults with **diabetes** mellitus, patients were **treated** chronically with Viagra (RTM; sildenafil citrate) in an out-patient multicenter study. Subjects were taking several different glucose lowering agents (including **metformin**, insulin or sulfonylureas) or were **treated** with diet alone. Glycosylated hemoglobin (HbA1c), a recognized measure of chronic glucose **control**, was determined prior to the study. Significant improvements in glucose **control** was observed in patients **treated** with Viagra (RTM). Improvements were consistently observed across the subject group irrespective of their background **therapy**.

MECHANISM OF ACTION - cGMP PDE-5 **Inhibitor**.

(I) had an IC50 value of less than 100 nM against PDE-5 and a selectivity ratio of PDE-5 over PDE-3 of more than 100 (claimed).

USE - (I) Is useful for curative, palliative or prophylactic **treatment** of insulin resistance syndrome (i.e. existence of 2 or more of **dyslipidemia**, **hypertension**, type II **diabetes** mellitus (preferred), **impaired glucose tolerance** (**IGT**) (preferred), family history of **diabetes**, **hyperuricemia** and/or gout, a procoagulant state, **atherosclerosis**, or truncal obesity (claimed).

Dwg.0/0

L22 ANSWER 14 OF 15 WPIDS (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 2001-281809 [29] WPIDS
DOC. NO. CPI: C2001-085742
TITLE: Combination used for treating diabetes and metabolic disorders comprises nateglinide, antidiabetic phenylacetic acid derivative or acarbose and carrier.
DERWENT CLASS: B05
INVENTOR(S): BALL, M; DUNNING, B; GATLIN, M R; PONGOWSKI, M
PATENT ASSIGNEE(S): (NOVS) NOVARTIS AG; (NOVS) NOVARTIS-ERFINDUNGEN VERW GES MBH
COUNTRY COUNT: 95
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2001026639	A2	20010419	(200129)*	EN	28

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TZ UG ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW

AU 2001011339 A 20010423 (200147)

EP 1218015 A2 20020703 (200251) EN

R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE

WO 2001026639 A2	WO 2000-EP9816	20001006
AU 2001011339 A	AU 2001-11339	20001006
EP 1218015 A2	EP 2000-972695	20001006
	WO 2000-EP9816	20001006

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 2001011339 A	Based on		WO 200126639
EP 1218015	A2	Based on	WO 200126639

PRIORITY APPLN. INFO: US 1999-415308 19991008; US 1999-415307 19991008

AN 2001-281809 [29] WPIDS

AB WO 200126639 A UPAB: 20010528

NOVELTY - Combination (I) comprises **nateglinide**, an antidiabetic phenylacetic acid derivative or acarbose or their salts and optionally at least one carrier for simultaneous, separate or sequential use.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is included for a commercial package comprising (I) together with instructions for the delay of progression or **treatment** of metabolic disorders or a **method** of improving bodily appearance.

ACTIVITY - Antidiabetic; antilipemic; antiulcer; antiinflammatory; vasotropic; hypotensive; cardiant; antiarthritic; osteopathic; cerebroprotective; anorectic; gastrointestinal; ophthalmological; muscular; dermatological.

MECHANISM OF ACTION - None given.

USE - Used for **treating diabetes**, conditions associated with **diabetes**, especially type 2 **diabetes** mellitus and metabolic disorders e.g. hyperglycemia, hyperinsulinaemia, **hyperlipidemia**, insulin resistance, impaired glucose metabolism, obesity, diabetic **retinopathy**, macular degeneration, cataracts, diabetic **nephropathy**, glomerulosclerosis, diabetic neuropathy, erectile dysfunction, premenstrual syndrome, vascular restenosis and ulcerative colitis, coronary heart disease, **hypertension**, angina pectoris, myocardial infarction, stroke, skin, connective tissue disorders, foot ulcerations, metabolic acidosis; arthritis, osteoporosis and conditions of **impaired glucose tolerance**

ADVANTAGE - The **nateglinide** and phenylacetic acid derivative show a synergistic effect.

Dwg.0/0

L22 ANSWER 15 OF 15 WPIDS (C) 2003 THOMSON DERWENT

ACCESSION NUMBER: 2000-271226 [23] WPIDS

DOC. NO. CPI: C2000-082736

TITLE: Composition comprising an anti-diabetic agent and a bioavailable source of chromium and/or vanadium is used for improving glucose metabolism, reducing hemoglobin A1c (HbA1c) levels, and treating diabetes.

DERWENT CLASS: B03 B05 B07 D16

INVENTOR(S): FINE, S; KINSELLA, K; FINE, S A; KINSELLA, K J

PATENT ASSIGNEE(S): (AKES-N) AKESIS PHARM INC

COUNTRY COUNT: 88

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG

WO 2000015211 A2 20000323 (200023)* EN 81
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZA ZW
AU 9960446 A 20000403 (200034)
EP 1113804 A2 20010711 (200140) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI
US 6376549 B1 20020423 (200232)

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000015211	A2	WO 1999-US21377	19990917
AU 9960446	A	AU 1999-60446	19990917
EP 1113804	A2	EP 1999-969024	19990917
		WO 1999-US21377	19990917
US 6376549	B1	US 1998-156102	19980917

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9960446	A	Based on	WO 200015211
EP 1113804	A2	Based on	WO 200015211

PRIORITY APPLN. INFO: US 1999-126489P 19990326; US 1998-156102 19980917

AN 2000-271226 [23] WPIDS

AB WO 200015211 A UPAB: 20000516

NOVELTY - Composition (I) comprising an anti-diabetic agent and a bioavailable source of chromium is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:

(a) a composition (II) comprising an anti-diabetic agent and a bioavailable source of vanadium;

(b) a **method** for improving glucose metabolism comprising the administration of (I) or (II);

(c) a kit for improving glucose metabolism in a subject comprising an ingestible formulation of (I) or (II), and instructions for the administration of the ingestible formulation.

ACTIVITY - Glucose metabolism modulator; hypoinsulinemic; hypoglycemic; antidiabetic; antilipemic; hypotensive; cardiant; anoretic.

In a female subject suffering from Type 2 **diabetes** experiencing poor blood sugar **control** while taking **metformin** (500 mg; multiply 2/day), an additional oral composition comprising chromium (333 mcg; in the form of chromium picolinate/polynicotinate), magnesium (46 mg; in the form of 384 mg magnesium chloride); vanadyl sulfate hydrate (100 mg), vitamin E (400 I.U.), and folate (400 mcg) was administered. The results for the Hemoglobin A1c (HbA1c) level, estimated blood sugar (mg/dl) and fasting blood sugar (mg/dl) were 7.9, 141 and 153 for the combination of **metformin** and the oral composition, and 9.7, 200, and 185 for **metformin** alone.

MECHANISM OF ACTION - Insulinotropic

USE - (I) and (II) are used in regulating or improving glucose metabolism (claimed), **preventing** or reducing insulin resistance, beta cell attrition, hyperinsulinemia, hyperglycemia, hepatic gluconeogenesis, elevated hemoglobin A1c (HbA1c) levels (claimed), blood glucose levels, and **diabetes** (claimed), diabetic symptoms and related disorders e.g. Type 1, Type 2 **diabetes**, maturity-onset **diabetes** of youth (MODY), **impaired glucose tolerance** (**IGT**), and related sequelae. (I) and (II) are used for modulating lipid metabolism e.g. body fat stores, blood pressure or hyperlipoproteinemia, reducing the severity of **dyslipidemia**, **atherosclerosis** and congenital heart disease (CHD) and reducing the appetite e.g. for cosmetic reasons or obesity. (I) and (II) are used in prognostic **methods** to determine whether a subject is at risk of developing **diabetes** e.g. from Type 2 **diabetes**.

ADVANTAGE - (I) and (II) stimulate the production of insulin and increase the half life or the potency of insulin in vivo. The composition acts synergistically improving glucose metabolism more than the use of e.g. **metformin** alone.

Dwg.0/0

L4 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:489226 HCAPLUS
DOCUMENT NUMBER: 135:56079
TITLE: Use of a hypoglycemic agent for treating impaired glucose metabolism
INVENTOR(S): **Guitard, Christiane; Muller, Beate ; Emmons, Rebecca**
PATENT ASSIGNEE(S): Novartis A.-G., Switz.; Novartis-Erfindungen Verwaltungsgesellschaft m.b.H.
SOURCE: PCT Int. Appl., 26 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001047514	A1	20010705	WO 2000-EP12174	20001204
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1239854	A1	20020918	EP 2000-990641	20001204
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
US 2001016586	A1	20010823	US 2000-731139	20001206
NO 2002002979	A	20020620	NO 2002-2979	20020620

PRIORITY APPLN. INFO.: EP 1999-125761 A 19991223
WO 2000-EP12174 W 20001204

AB The invention discloses the use of a hypoglycemic agent, or a pharmaceutically acceptable salt thereof, for the manuf. of a medicament for the prevention or delay of the progression to overt diabetes, esp. type 2, prevention or redn. of microvascular complications (e.g. retinopathy, neuropathy, nephropathy), prevention or redn. of excessive cardiovascular morbidity (eg. myocardial infarction, arterial occlusive disease, atherosclerosis and stroke) and cardiovascular mortality, prevention of cancer and redn. of cancer deaths. Addnl., the invention relates to the use of a treatment for diseases and conditions that are assocd. with impaired glucose metab., impaired glucose tolerance, or impaired fasting glucose. Formulations of nateglinide are included.

REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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L4 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2003 ACS
IC ICM A61K031-198
ICS A61P005-50
CC 1-10 (Pharmacology)

ST impaired glucose metab treatment hypoglycemic agent; nateglinide pharmaceutical impaired glucose metab; diabetes complication hypoglycemic agent

IT Heart, disease
(angina pectoris; hypoglycemic agent for treating impaired glucose metab.)

IT Antiarteriosclerotics
(antiatherosclerotics; hypoglycemic agent for treating impaired glucose metab.)

IT Brain, disease
(cerebrovascular; hypoglycemic agent for treating impaired glucose metab.)

IT Artery, disease
(coronary; hypoglycemic agent for treating impaired glucose metab.)

IT Pregnancy
(diabetes during; hypoglycemic agent for treating impaired glucose metab.)

IT Eye, disease
(diabetes-assocd.; hypoglycemic agent for treating impaired glucose metab.)

IT Blood vessel, disease
(diabetic angiopathy; hypoglycemic agent for treating impaired glucose metab.)

IT Blood vessel, disease
(diabetic microangiopathy; hypoglycemic agent for treating impaired glucose metab.)

IT Kidney, disease
(diabetic nephropathy; hypoglycemic agent for treating impaired glucose metab.)

IT Nerve, disease
(diabetic neuropathy; hypoglycemic agent for treating impaired glucose metab.)

IT Eye, disease
(diabetic retinopathy; hypoglycemic agent for treating impaired glucose metab.)

IT Metabolism, animal
(disorder; hypoglycemic agent for treating impaired glucose metab.)

IT Lipids, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(dyslipidemia; hypoglycemic agent for treating impaired glucose metab.)

IT Diabetes mellitus
(family history; hypoglycemic agent for treating impaired glucose metab.)

IT Drug delivery systems
(galenical; hypoglycemic agent for treating impaired glucose metab.)

IT Necrosis
(gangrene; hypoglycemic agent for treating impaired glucose metab.)

IT Proteins, specific or class
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(glucagon-like protein 1, and agonists; hypoglycemic agent for treating impaired glucose metab.)

IT Aging, animal
Anti-ischemic agents
Antidiabetic agents

Antihypertensives
Antiobesity agents
Antitumor agents
Cardiovascular agents
Drug delivery systems
(hypoglycemic agent for treating impaired glucose metab.)

IT Sulfonylureas
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(hypoglycemic agent for treating impaired glucose metab.)

IT Heart, disease
(infarction; hypoglycemic agent for treating impaired glucose metab.)

IT Heart, disease
(ischemia; hypoglycemic agent for treating impaired glucose metab.)

IT Diabetes mellitus
(non-insulin-dependent; hypoglycemic agent for treating impaired glucose metab.)

IT Artery, disease
(occlusion; hypoglycemic agent for treating impaired glucose metab.)

IT Brain, disease
(stroke; hypoglycemic agent for treating impaired glucose metab.)

IT Drug delivery systems
(tablets; hypoglycemic agent for treating impaired glucose metab.)

IT 69-93-2, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(hyperuricemia; hypoglycemic agent for treating impaired glucose metab.)

IT 56-03-1D, Biguanide, derivs. 103-82-2D, Phenylacetic acid, derivs. 33342-05-1, Gliquidone 97322-87-7, Troglitazone 105816-04-4, Nateglinide 111025-46-8, Pioglitazone 122320-73-4, Rosiglitazone 135062-02-1, Repaglinide
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(hypoglycemic agent for treating impaired glucose metab.)

IT 50-99-7, D-Glucose, biological studies 9004-10-8, Insulin, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(hypoglycemic agent for treating impaired glucose metab.)

IT 54249-88-6, dipeptidyl peptidase IV
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; hypoglycemic agent for treating impaired glucose metab.)

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